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Health-Related Quality of Life and Costs in Prostate Cancer



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***HEALTH-RELATED QUALITY OF LIFE AND COSTS IN
PROSTATE CANCER***

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ACADEMIC DISSERTATION

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*“As we know, there are known knowns; there are things we know we know.
We also know there are known unknowns; that is to say we know there are some things we
do not know. But there are also unknown unknowns—the ones we don’t know we don’t
know.”*

Donald Rumsfeld, 2002

Abstract

Scientific evidence based on health economic evaluations is needed to enable decisions-makers to make informed decisions on resource allocations within health care systems. Usually the economic evaluations take place within health technology assessment (HTA) framework. The use of health economic evaluations has increased during the last two decades and will hopefully contribute towards making the best possible use of limited health care resources.

Prostate cancer (PC) is the most frequently diagnosed cancer in men accounting for 29% of all the cancers diagnosed in men in Finland. There are almost 50,000 men in Finland currently living with PC. The prevalence of PC is expected to rise with aging population and improved diagnostics and treatment options. This may also increase the burden from PC on the society and, consequently, resource optimization is warranted.

Health-related quality of life (HRQoL) assessments in PC is an evolving field but, based on the literature, the use of preference-based single index measures to generate health state utilities or values valid for the estimation of quality adjusted life years (QALY) gained, is scarce. This is problematic, as health state utility estimates are an integral component of cost-utility analysis, which can be considered the gold standard analytical method in health economics today.

The general aim of this thesis was to study HRQoL and costs in different states of PC. This was done from the perspective of generating evidence that can be used for the health economic analysis. HRQoL was assessed with one cancer-specific (EORTC QLQ-C30) and two generic (EQ-5D-3L and 15D) HRQoL instruments. The EQ-5D-3L also included visual analogue scale (VAS). In addition, costs were also collected for these patients as incremental costs compared to age, gender and place of residence standardised peers.

A total of 1025 PC patients were invited to study, of whom 630 (61.5%) responded. Patients were collected in the Helsinki and Uusimaa Hospital District in a cross-sectional setting. PC data were collected as a part of a larger study, where similar data were also collected for colorectal cancer (CRC) and breast cancer (BC). PC patients ages ranged from 44 to 93 years and most of them had local disease and were married or cohabiting and had higher education. Patients were divided into five mutually exclusive groups based on disease state: *Primary* (local disease, first six months after diagnosis), *Rehabilitation* (local disease, 0.5 – 1.5 years after diagnosis or recurrence), *Remission* (local disease, more than 1.5 years after diagnosis), *Metastatic* (after detection of metastases) and *Palliative care* (no chemo- or radiotherapy and patients who died due to cancer within six months of responding).

All evaluated HRQoL instruments provided valuable insight into patients' overall HRQoL. The 15D scores of the study population ranged from 0.344 to 1.000 (mean 0.863), the EQ-5D: -0.166 to 1.000 (mean 0.845), and the VAS: 1 to 100 (mean 76.4). 30 patients reported having perfect/full health (5%) with the 15D and VAS, whereas 266 (42%) patients had same result with the EQ-5D. HRQoL remained on a relatively high level until the disease progressed. Symptoms of fatigue and pain, and the background variables of financial difficulties and age, were the most important factors associated with poor HRQoL.

Current understanding of patients' HRQoL in terminal stages of cancer is limited. In this study 311 palliative cancer patients were invited to participate and out of those 114 patients (37%) responded. This palliative cancer patient data set included 30 PC patients, 57 CRC patients and 27 BC patients. The mean utility scores varied widely depending on the HRQoL instrument used: the 15D gave the highest utility values (mean 0.74), followed by the EQ-5D-3L (0.59) and VAS (55.0). The mean utility value among PC patients was 0.67 with the 15D, 0.59 with the EQ-5D-3L, and 48.7 with the VAS. With the EQ-5D-3L, 13% of the patients received perfect health status (ie., EQ-5D-3L score 1.00).

Direct costs related to different states of PC are significant. In this study, costs are reported as incremental costs due to cancer for a six-month period and they include direct medical costs, productivity costs and costs of informal care. Resource use and cost data were retrieved from various registries and in addition patients answered background questions concerning informal care, work capacity and educational status. To analyse incremental cost burden due to cancer, two age, gender and place of residence standardised control subjects were extracted from the Social Insurance Institution's electronic records.

Costs differed markedly between the states of disease. Mean direct health care costs for the six-month periods were: *Primary* treatment state €2750, *Rehabilitation* state €1143, remission state €760 and *Metastatic* state €7423. Most of the patients were not working which was expected due to their mean age. 102 (16.7%) of the patients were employed and of the 430 retired patients more than two-thirds were eligible for the state pension based on their age of 65 years or more. Only 18 (2.9%) patients received disability pension due to their cancer and 28 patients (4.6%) received disability pension due to other reasons. Seventeen patients (2.8%) reported not working or being unemployed. The number of days absent from work due to sick leave was relatively low, being on the average less than one day during the six-month period, however, the mean number days being absent from the work due to early retirement was much higher. Combined total days absent from the work were highest in *Primary* (8.2 days) and *Metastatic* (12.5 days) groups and lowest in *Rehabilitation* and *Remission* groups, 5.4 and 4.0 days, respectively.

Productivity costs were therefore highest (€4277) in the metastatic state. Overall, the average share of indirect costs was around one third of the total costs. However, when including informal care, their combined share of the total costs increased to around half or more. The mean number of informal care received from patient's family or others was modest around one hour or less per week, and it was reported only by 34 patients (5.6%). Based on study results productivity losses and costs of informal care can play a major role when estimating the total economic burden of PC. Excluding such a large share of costs from assessments might have a significant impact on the decision making process of health economic evaluations or HTA.

The single-index HRQoL instruments considered here (EQ-5D-3L and 15D) should not be considered interchangeable in health economic evaluations, especially in the case where HRQoL values are low or differ significantly from those of age-standardised peers. The EQ-5D-3L produces greater differences in utilities than the 15D. Some of the earlier studied issues like the marked ceiling effect, two-peaked, discontinuous distribution of the EQ-5D scores, as well as the higher HRQoL scores obtained by the 15D compared to EQ-5D-3L were also evident from the PC material. Thus, these

differences need to be taken into consideration when these instruments and their results are used in health economic evaluations.

Tiivistelmä

Terveystaloudellisiin arviointeihin perustuvaa tieteellistä näyttöä tarvitaan, jotta päätöksentekijät voivat tehdä perusteltuja päätöksiä resurssien kohdentamisesta terveydenhuoltojärjestelmissä. Arvioinneissa tiivistetään ja arvioidaan tutkimusnäyttöä hoitojen hyödyistä, haitoista, kustannuksista ja kustannusvaikuttavuudesta muihin hoitovaihtoehtoihin verrattuna. Tutkimusnäytön kokoamisessa ja arvioinnissa hyödynnetään terveysteknologian arvioinnin lähestymistapoja (HTA). Terveystaloudellisten arvioiden käyttö on kasvanut viimeisten kahden vuosikymmenen aikana ja nämä ovat osaltaan tukeneet niukkojen terveydenhuollon resurssien mahdollisimman tehokasta hyödyntämistä.

Eturauhassyöpä (PC) on yleisimmin todettu syöpä miehillä, mikä vastaa 29 prosenttia kaikista miehillä Suomessa diagnosoiduista syöpätaudeista. Suomessa on tällä hetkellä lähes 50 000 eturauhassyövän kanssa elävää miestä. Taudin esiintyvyyden odotetaan kasvavan väestön ikääntyessä ja diagnostiikka- ja hoitovaihtoehtojen parantuessa. Tämä tulee lisäämään tautitaakkaa yhteiskunnalle, ja näin ollen terveydenhuollon resurssien tehokas kohdentaminen on tärkeää.

Terveysteen liittyvän elämänlaadun (HRQoL) tutkimus eturauhassyövässä on yleistymässä, mutta kirjallisuuden perusteella preferenssipohjaisten indeksimittareiden, jotka tuottavat terveyden tiloihin sidottuja hyötyjä (utiliteetteja), tai joita voidaan käyttää laatupainotettujen lisäelinvuosien (QALY) määrittämiseen, on vähäistä. Tämä on ongelmallista, koska elämänlaatuarviot ovat olennainen osa kustannus-hyötyanalyysejä, jota voidaan pitää nykyään tarkoituksenmukaisimpana analyysimenetelmänä terveystaloustieteessä.

Tämän tutkimuksen yleisenä tavoitteena oli tutkia terveyteen liittyvää elämänlaatua ja kustannuksia eturauhassyövän eri vaiheissa. Tarkoituksena oli tuottaa tietoa, jota voidaan käyttää terveystaloustalouden analyysien tuottamiseksi. Terveysteen liittyvää elämänlaatua arvioitiin yhdellä syöpäspesifisellä (EORTC QLQ-C30) ja kahdella geneerisellä (EQ-5D-3L ja 15D) elämänlaatumittarilla. EQ-5D-3L sisälsi myös visuaalisen mittarin (VAS). Kustannuksia arvioitiin lisäkustannuksina potilaille haettujen ikä-, sukupuoli- ja asuinpaikan mukaan vakioitujen vertaisarviointien perusteella.

Tutkimukseen kutsuttiin yhteensä 1025 eturauhassyöpäpotilasta, joista 630 (61,5 %) osallistui tutkimukseen. Potilaat kerättiin poikkileikkausotoksena Helsingin ja Uudenmaan sairaanhoitopiiristä. Eturauhassyöpäpotilaiden tiedot koottiin osana laajempaa tutkimusta, jossa samankaltaisia tietoja kerättiin myös paksusuoli- (CRC) ja rintasyöpäpotilailta (BC). Eturauhassyöpäpotilaiden ikäjakauma vaihteli 44-vuodesta 93-vuoteen, useimmilla heistä oli paikallinen sairaus, he olivat naimisissa tai avoliitossa ja heillä oli korkeakoulutus. Potilaat jaettiin viiteen toisensa poissulkeviin ryhmiin, jotka perustuivat syövän eri tiloihin: *Primaari* (paikallinen sairaus, kuusi kuukautta diagnoosin jälkeen), *Rehabilitation* (paikallinen sairaus, 0,5 - 1,5 vuotta diagnoosin tai toistumisen jälkeen), *Remission* (paikallinen sairaus, yli 1,5 vuotta diagnoosista), *Metastatic* (metastaasien havaitsemisen jälkeen) ja *Palliative* (ilman kemoterapiaa ja sädehoitoa sekä potilaita, jotka kuolivat syöpään kuuden kuukauden sisällä).

Kaikki arvioidut elämänlaatumittarit antoivat arvokasta tietoa potilaan terveyteen liittyvästä elämänlaadusta. 15D elämänlaatumittarin arvot vaihtelivat välillä 0,344 – 1,000 (keskiarvo 0,863),

EQ-5D: -0,166 – 1,000 (keskiarvo 0,845) ja VAS: 1 - 100 (keskiarvo 76,4). 30 potilasta arvioi olevansa täydellisessä terveydentilassa (5 %) käyttäen 15D- ja VAS-mittaria, kun taas EQ-5D-3L mittari tuotti jopa 266 (42 %) potilaalle vastaavan tuloksen. Terveyteen liittyvä elämänlaatu pysyi suhteellisen korkealla tasolla, kunnes sairaus eteni. Tärkeimmät elämänlaatua laskevat selittävät tekijät olivat väsymyksen ja kivun oireet sekä taloudelliset ongelmat ja korkea ikä.

Nykyinen tietämys potilaan kokemasta elämänlaadusta syövän loppuvaiheissa on rajallista. Tässä tutkimuksessa tavoitettiin 311 palliatiivista syöpäpotilasta ja näistä 114 (37 %) osallistui tutkimukseen. Palliatiivisessa hoidossa oleva potilasjoukko sisälsi 30 eturauhassyöpäpotilasta, 57 paksunsuolensyövän- ja 27 rintasyöpäpotilasta. Keskimääräiset elämänlaatuarvot palliatiivisilla potilailla vaihtelivat suuresti riippuen käytetystä elämänlaatumittarista: 15D tuotti korkeimmat arvot (keskiarvo 0,74), jota seurasivat EQ-5D-3L (0,59) ja VAS (55,0). Palliatiivisten eturauhassyöpäpotilaiden keskimääräiset elämänlaadun arviot olivat puolestaan 0,67 käyttäen 15D mittaria, 0,59 EQ-5D-3L-mittarilla ja 48,7 VAS-mittarilla. Palliatiivisessa hoidossa olevista potilaista käyttäen EQ-5D-mittaria 13 % potilaista oli täydellisessä terveydentilassa (EQ-5D-3L-pisteet 1,00).

Eturauhassyövän taudin tiloihin liittyvät suorat kustannukset olivat merkittäviä. Kustannuksia arvioitiin syövän aiheuttamina lisäkustannuksina kuuden kuukauden ajanjaksoina ja ne sisälsivät suorat sairauskulut, tuottavuuden menetykset ja epävirallisen hoidon kustannukset. Resurssien käyttö- ja kustannustiedot noudettiin eri rekistereistä, ja lisäksi potilaat vastasivat taustakysymyksiin epävirallisesta hoidosta, työkyvystä ja koulutustaustasta. Syövän aiheuttamien lisäkustannusten analysoimiseksi jokaiselle potilaalle poimittiin kaksi ikä, sukupuoli ja asuinpaikka vakioituja verrokkeja Kansaneläkelaitoksen rekisteristä.

Eturauhassyövästä johtuvat kustannukset erosivat selvästi tautitilojen välillä. Keskimääräiset terveydenhuollon välittömät kustannukset kuuden kuukauden jaksoina eri tautitiloissa olivat: *Primary* 2750 €, *Rehabilitation* 1143 €, *Remission* 760 € ja *Metastatic* 7423 €. Suurin osa potilaista oli työelämän ulkopuolella, mikä oli odotettavissa keskimääräisen korkean iän perusteella. Potilaista 102 (16,7 %) oli työssä, ja 430 eläkkeellä olevasta potilaasta yli kaksi kolmasosaa oli 65 vuotta täyttäneitä ja siten valtioneläkkeeseen oikeutettuja. Vain 18 (2,9 %) potilasta oli saanut syöpään liittyvän työkyvyttömyyseläkkeen ja 28 potilasta (4,6 %) oli saanut työkyvyttömyyseläkkeen muusta syystä. 17 potilasta (2,8 %) ilmoitti olevansa työssä tai työttömänä.

Sairauspoissaoloista johtuvien menetettyjen työpäivien määrä oli suhteellisen alhainen, keskimäärin alle yhden päivän kuuden kuukauden aikana, kun taas varhaiseläkkeestä johtuva työstä poissaoloaika oli huomattavasti korkeampi. Yhdistetty työstä poissaolo oli suurinta *Primaari*- (8,2 päivää) ja *Metastatic*-ryhmissä (12,5 vrk) ja alhaisimmillaan *Rehabilitation*- ja *Remission*-ryhmissä, 5,4 ja 4,0 vuorokautta.

Menetykset tuottavuuskustannuksina olivat korkeimmat (4277 €) edenneessä taudissa. Kaiken kaikkiaan epäsuorien kustannusten osuus kokonaiskustannuksista oli noin kolmasosa. Yhdistäen tuotannonmenetyksen ja epävirallisen hoidon kustannukset, niiden yhteenlaskettu osuus kokonaiskustannuksista nousi noin puoleen tai hieman yli. Potilaan läheisten antaman keskimääräinen epävirallisen hoidon määrä oli vaatimaton noin tunnin tai vähemmän viikossa, ja vain

34 potilasta (5,6 %) ilmoitti saaneensa sitä. Tutkimustulosten perusteella tuottavuuden menetykset ja epävirallisen hoidon kustannukset voivat olla merkittävässä roolissa arvioitaessa eturauhassyövän kokonaiskustannuksia. Näiden kustannusten huomioita jättämisellä voi olla merkittävä vaikutus taloudellisten arvioiden tai HTA:n lopputulokseen ja täten mahdollisiin resurssikohdennuspäätöksiin.

Tutkimuksessa analysoituja geneerisiä elämänlaatumittareita (EQ-5D-3L ja 15D) ei tulisi käyttää taloudellisissa arvioinneissa suoraan keskenään vaihdettavina etenäkään silloin, kun elämänlaatuarvot ovat alhaiset tai eroavat huomattavasti ikävakioitujen vertaisten tasosta. EQ-5D-3L tuottaa suurempia eroja kuin 15D. Tämän tutkimuksen tulokset tukevat osaltaan joitain jo aiempia tutkimuksia, kuten EQ-5D-mittarin korkean kattoefektin, kaksihuippuisen, epäjatkuvan tulosten jakauman sekä 15D-mittarin tuottamat korkeammat elämänlaatuarvot verrattuna EQ-5D-3L-mittariin. Nämä erot on syytä ottaa huomioon valittaessa ja käytettäessä näitä mittareita sekä varsinkin analysoitaessa niiden tuottamia tuloksia.

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List of appendices

Appendix 1. Questionnaire
Appendix 2. Published articles

List of original publications

This dissertation is based on the following articles, which are referred to in the text by the numerals I, II, III and IV. Unpublished data are also presented.

- I Torvinen S, Färkkilä N, Sintonen H, Saarto T, Roine RP, Taari K. 2013. Health-related quality of life in prostate cancer *Acta Oncologica* 52(6):1094-101.

- II Färkkilä N*, Torvinen S*, Roine RP, Sintonen H, Hänninen J, Taari K, Saarto T. 2014. Health-related quality of life among breast, prostate, and colorectal cancer patients with end-stage disease. *Qual Life Res.* 23(4):1387-94.

- III Torvinen S, Färkkilä N, Roine RP, Sintonen H, Saarto T, Taari K. 2016. Costs in different states of prostate cancer. *Acta Oncologica* 55(1):30-7.

- IV Torvinen S*, Bergius S*, Roine RP, Lodenius L, Sintonen H, Taari K. 2016. Use of patient assessed health-related quality of life instruments in prostate cancer research: A systematic review of the literature 2002-2015. *Int J Technol Assess Health Care*.32(3):97-106.

* Authors share equal contribution

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Abbreviations

ADT	androgen deprivation therapy
BC	breast cancer
BPH	benign prostatic hyperplasia
CAB	combined androgen blockade
CBA	cost-benefit analysis
CEA	cost-effectiveness analysis
CMA	cost-minimization analysis
COI	cost of illness
CRC	colorectal cancer
CUA	cost-utility analysis
DRE	digital rectal exam
EORTC	European organisation for research and treatment of cancer
EPIC	expanded prostate cancer index composite
ERSPC	European randomized study of screening for prostate cancer
FACT-G	functional assessment of cancer therapy - general
FACT-P	functional assessment of cancer therapy - prostate
FCA	friction cost approach
HCA	human capital approach
GDP	gross domestic product
HRQoL	health related quality of life
HTA	health technology assessment
HUI2/3	health utility index 2/3
ICD	international statistical classification of diseases and related health problems
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
IMRT	intensity modulated radiation therapy
IPSS	international prostate symptoms score
M	million
mCRPC	metastatic castration resistant prostate cancer
NICE	national institute for health and care excellence
OLS	ordinary least squares
PC	prostate cancer
PSA	prostate specific antigen
QALY	quality-adjusted life-year
QWB	quality of well-being scale
RCT	randomised clinical trial
SF-36	short form 36
SF-6D	short form six dimension
SG	standard gamble
SRE	skeletal-related events
SII	social insurance institution of Finland
TTO	time trade-off
VAS	visual analogue scale
WTP	willingness to pay

1. INTRODUCTION

European health care systems are struggling with challenges on how to fund health care with ever raising needs of the patients. Scientific evidence based on health economic evaluations has been introduced to enable decisions-makers to make informed decisions on resource allocation. The use of health economic evaluations has increased with the aim of making the best possible use of limited health care resources (Drummond et al 2005).

Health economics is a discipline under the umbrella of economics. Health economics usually deals with issues related to efficiency, effectiveness, value, equity and behaviour in the production and consumption of health and healthcare. Some of the topics in this dissertation could be also linked to pharmacoeconomics, which is a multidisciplinary discipline interested in the clinical and economic aspects of pharmaceuticals within the health care systems or society and uses methods originating from health economics.

Prostate cancer (PC) is the most common non-skin cancer in men and the third most common cause of cancer deaths in men in Western Europe. In 2012, an estimated 1.1 million men worldwide were diagnosed with PC, accounting for 15% of the cancers diagnosed in men (Ferlay et al 2013). Most cases (around 70%) are diagnosed in more developed regions and the burden of PC is remarkable both in economic and clinical respects.

During the last few decades, increased attention has been focused on cancer patients' health-related quality of life (HRQoL), but so far the understanding of patients' HRQoL and costs of care throughout the disease pathway from early diagnosis to the terminal stages of cancer is still limited. This is partly explained by the fact that generic HRQoL instruments that can be used for cost-utility analysis, the state-of-the-art method of health economic evaluation, have only seldom been used among PC patients. This study aimed to collect this type of evidence to support cost-utility analyses in PC.

For the comparison of the results from health economic evaluations, a key question is to know whether different HRQoL instruments produce similar results. If they do not, it may have a significant impact on the results of cost-utility analyses and potentially mislead resource allocation decisions.

2. BACKGROUND AND REVIEW OF THE LITERATURE

2.1 *Prostate cancer*

Prostate cancer (PC), also known as carcinoma of the prostate, is the development of cancer in the prostate, a gland in the male reproductive system. In contrast to the current situation, PC was initially considered a rare disease, probably because of shorter life expectancies and poorer detection methods in the 19th century (Lytton 2001).

Today PC is the fourth most common cancer in both sexes combined and the second most common cancer in men after skin cancer. PC accounts for 15% of the cancers diagnosed in men (Bray et al 2013). Factors that increase the risk of PC include: older age, a family history of the disease, and race, as African American men are approximately 70% more likely to develop prostate cancer in their lifetime than Caucasian or Hispanic men. About 99% of cases occur in those over the age of 50. Having a first-degree relative with the disease increases the risk two- to threefold. Other factors that may be involved include a diet high in processed meat, red meat, or milk products or low in certain vegetables (World Health Organization 2014). Studies of twins in the Nordics countries suggest that around half of PC risk can be explained by inherited factors (Mucci et al 2016).

Due to risk factors, the incidence of PC is higher in developed countries than in the rest of the world. In fact, the incidence of PC varies more than 25-fold across the world; being highest in Australia/New Zealand, Northern America and in Western and Northern Europe, because the practice of prostate-specific antigen (PSA) testing and subsequent biopsy has become widespread in those areas (Bray et al 2013).

Therefore, a majority of those with PC will, due to their advanced age at diagnosis, die of other causes without suffering significantly from PC. Also, PSA testing has a much greater effect on the incidence than on mortality; there is less variation in mortality rates worldwide (ten-fold) than is observed for incidence, with the number of deaths from PC being larger in less developed than in more developed countries (Bray et al 2013).

The time between screen detection (PSA testing) and clinical detection of a cancer is called lead time, which is an important concept for early detection of cancer. Long lead times may lead to over-diagnosis, and conversely with short lead times, it can be difficult to ensure that screening takes place in the short window between when a cancer is first amenable to screen detection and when it is detected clinically. In a recent Swedish study, men with a longer lead time between elevated PSA and subsequent prostate cancer diagnosis were more likely to have high-grade cancers at diagnosis (Assel et al 2018). This finding supports the grade progression hypothesis, whereby PC followed over time exhibits a transition from benign to low-grade and then to high-grade cancer. However, it is not possible to know whether a given low grade lesion becomes high-grade cancer, or whether a new high-grade focus arises in a prostate that already contains a low-grade cancer.

Most PCs are slow growing; however, some grow relatively quickly. The cancer cells may spread from the prostate to other parts of the body, particularly the bones and lymph nodes. PC may initially cause no symptoms, however in later stages it can lead to difficulty in urinating, blood in the urine, or pain in the pelvis, back or when urinating. Other late symptoms may include feeling tired due to anemia (World Health Organization 2014).

Incidence and prevalence in Finland

In 2015, 4,855 new PC cases were diagnosed in Finland (Finnish Cancer Registry 2016). It was the most frequently diagnosed cancer in men in Finland accounting for 29% of all the cancers diagnosed in men. The incidence of PC has been steadily rising over the years and the annual number of new diagnoses has doubled over the last 50 years. This has been mainly driven by more advanced diagnostic methods and aging of the population. In the beginning of year 2015, there were 47,500 men living with diagnosed PC (ICD code C61) in Finland. In year 2015 PC caused 921 deaths, being the second most common cause of cancer deaths (14.0%) in men after lung cancer. The PC incidence is expected to increase up to approximately 6,400 cases and slightly over 1,000 PC deaths by year 2020 (Ferlay et al 2013).

Screening and diagnostics of prostate cancer

Early PC is usually a non-symptomatic disease, or if there are symptoms, they are similar to those caused by benign prostatic enlargement. Most cases are found during screening with a PSA blood test, or sometimes with a digital rectal exam (DRE), but the actual diagnosis can only be made with a prostate biopsy. In the DRE the examiner inserts a gloved, lubricated finger into the rectum to examine the adjoining prostate. The PSA blood test measures the concentration of this molecule in the blood. PSA testing was introduced to evaluate treatment response in late 1980s, but was soon widely adopted for screening (Hayes & Barry 2014).

Finnish researchers have participated in the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial to evaluate the impact of PC screening on mortality. Based on the results of 262,000 people during a nine-year follow-up, it seems that PSA testing reduces deaths from PC by one fifth (Schröder et al 2009). Of the Finnish participants (80,000) of the trial, 30,000 were randomized to have PSA testing at the age of 55-71 years 2-3 times at four-year intervals. The remaining men formed the control group. The incidence of PC in the screening arm was 8.8 per 1,000 person-years and in the control arm 6.6. PC mortality among the Finnish participants did not differ in a statistically significant manner between the arms and to avoid one PC death, around 1,200 men needed to be invited to screening and 25 PC cases detected. The Finnish study group concluded that a relatively conservative screening protocol produced a small PC-specific mortality reduction, however statistically not significant, in the Finnish trial, at the cost of moderate over-diagnosis (Kilpeläinen et al 2013).

The biggest benefit of screening is definitively its ability to detect PC at an early stage, when it can still be cured. In line with that, many more PCs were detected in the screened group than in the control group in the ERSPC study. Similar findings have also been reported in some other studies

indicating that not all early stage tumors will ever advance to harmful cancer (Carlsson et al 2015). Based on the results, it is not certain whether screening causes more benefit or harm. A Cochrane review concluded that PC screening did not significantly decrease PC-specific mortality in a combined meta-analysis of five randomized clinical trials (RCTs) (Ilic et al 2013). Only one study (ERSPC) reported a significant 21% reduction of PC-specific mortality in a pre-specified subgroup of men aged 55-69 years. Pooled data demonstrated no significant reduction in PC-specific and overall mortality.

The most important disadvantage of screening for PC is the detection of indolent cases, i.e., cancers that would not have been found without screening and would not have caused any harm during the man's lifetime. Currently it is not possible to differentiate the detectable small, histologically malignant, but clinically benign PC from more aggressive forms that would spread and eventually cause death (Kilpeläinen et al 2015). Currently the European Association of Urology (EAU) recommends not to subject men to PSA testing without counselling them on the potential risks and benefits (Mottet et al 2017).

The total number of PSA tests taken in Finland is unknown. Based on the ERSPC study, 68% of Finnish men in the in control arm had at least one PSA test. Out of them, 22.1% received at least one positive PSA test, and 9.7% were diagnosed with PC (Kilpeläinen et al 2017). This population can be considered to be representative (age range 55-67) for the non-screened male population in Finland but the total number of PSA tests taken annually remains unknown. As only opportunistic testing is currently used in Finland, further research is needed to reveal what the impact of opportunistic testing and that of other reasons is on the development of PC incidence and prevalence.

Treatments

The treatment decision is made together with the patient according to patient characteristics, cancer classification and recurrence risk rate. The decision among treatment choices can be complicated as there are many different options, and for some of them long-term effectiveness data are scarce. Determining whether the cancer is confined to the prostate is a key factor in choosing the treatment. If this is the case, localised treatments aiming to cure the disease are in place, but if the cancer has spread, the goal of treatment is more likely to control the cancer rather than to cure it.

For localised PC, the recommended treatment is active surveillance, radical prostatectomy, radiation (+/- hormonal) therapy, or hormonal therapy. Metastatic PC patients are treated with hormonal therapy. The aim of treatment for castration resistant metastatic PC patients is to improve HRQoL and relieve symptoms (Duodecim 2014).

The treatment decision in localised PC is affected by risk grading (histopathology and PSA), patient's life expectancy (comorbidities, age, general wellbeing), patient preferences on treatments (e.g., potential side effects), and local conditions (distance to treatment facilities, available treatment options). In a study comparing active monitoring, radical prostatectomy, and external-beam radiotherapy for the treatment of clinically localised PC, at a median of 10 years, PC-specific mortality was low irrespective of the treatment assigned, with no significant difference between the treatments (Hamdy et al 2016).

In retrospective analyses radical prostatectomy has gained the most favourable position (Zelevsky et al 2010). In moderate and high risk localised PC surgery seems to prolong patients' expected length

of life, but in the low risk group this is not seen. This is probably explained by the very good prognosis in this patient group even without active treatment (Bill-Axelsson et al 2014; Vickers et al 2012; Wilt et al 2012). PC which extends beyond the prostate into the surrounding tissue, into other organs, or into distant parts of the body, is called advanced PC. Up to 40% of men with PC develop metastatic disease and a large share of them eventually develop resistance to androgen deprivation therapy (ADT), and progresses to metastatic castration resistant PC (mCRPC) (Australia Cancer Council 2015).

Some patients may not need to be treated immediately and instead would like to follow the active surveillance approach. This could be a good option if a patient wants to avoid possible side effects such as incontinence or impotence for as long as possible, or if the cancer is very small and expected to grow slowly.

Radical Prostatectomy (Laparoscopic, Retropubic, Robotic Radical Prostatectomy) removes the entire prostate gland, seminal vesicles and some surrounding tissue as a safety margin. This is usually performed for localised disease, but it will not guarantee that the cancer will not appear again.

Chemotherapy is a standard treatment option in all cancers, and PC is not an exception. Chemotherapy is usually used in metastatic disease, when the disease has spread outside of the prostate and hormone therapy has failed.

PC cells usually require testosterone to grow, and lowering androgen levels with *hormone therapy* can stop or slow cancer growth. Most of the PCs are initially responsive to hormone therapy, but unfortunately hormone therapy has significant side effects, such as a decrease in sexual desire and erectile dysfunction. It is usually recommended as the initial treatment for advanced cancers (Heidenreich et al 2014). Hormone therapy can also be administered in sequences based on PSA testing and this is called *intermittent hormone therapy*.

Radiation therapy uses high-energy radiation and particles to kill cancer cells. The two main types used in PC are *external beam radiation therapy* (3-D Conformal Radiation Therapy, Intensity Modulated Radiation Therapy [IMRT], Proton Beam Radiation Therapy, Cyberknife) and *brachytherapy*. External beam radiation therapy is focused from a source outside the body onto the area affected by cancer. Patients are treated five days per week over a period of seven to eight weeks with each treatment only taking a few minutes. In brachytherapy small radioactive pellets (seeds) are implanted into the prostate. The seeds are permanently placed in the prostate for a radiation period of weeks or months (permanent seed implant) or they are inserted for relatively short period of time and then withdrawn (temporary seed implant).

Alternative and complementary therapies (Diet, Nutrition, Supplements, Exercise, Stress Reduction, Asian Medicine) may be available and can be used to support patients, but evidence on their effectiveness is scarce (Rackley et al 2006; Bishop et al 2011; Huebner & Follmann 2013).

Survival

PC patients' age-standardised relative survival is high compared to some other cancers, being 99% after 1, 94% after 5, and 89% after 10 years (Finnish Cancer Registry 2016). The five-year survival rates of PC are in Finland the highest among all European countries (Allemanni et al 2015). Life

expectancy in advanced PC with metastases is around 2-3 years and the 5-year survival rate is around 30% (American Cancer Society 2014). In patients with mCRPC life expectancy is 6-18 months and can be prolonged by 2-5 months with chemotherapy (de Bono et al 2010; Fizazi et al 2012; Scher 2012; Parker et al 2013).

Cost of prostate cancer

Based on a literature review, most of the studies related to the burden of managing PC have been carried out within the United States (US) health care system (Sanyal et al 2013). The literature review revealed that there was a lack of methodological consensus (e.g., cost components evaluated were inadequately reported), which led to variation in direct costs between studies making comparisons difficult (Sanyal et al 2013). Nevertheless, results of economic analyses indicate significant direct cost of PC treatments. Direct costs comprise all consumption of resources resulting from a treatment or therapy and directly attributable to this. Table 1 illustrates cost estimates for PC from different countries.

Table 1. Cost and burden estimates for PC.

Country	1 st year cost	4-5 year cost	Total burden from PC per inhabitant
Italy	€6,600 ¹	€8,516 ²	€10 ³
United Kingdom	€3,171 ²	€5,984 ²	€7 ³
Germany	€4,057 ²	€10,949 ²	€21 ³
France	€5,851 ²	€9,725 ²	€15 ³
Spain	€3,256 ²	€7,753 ²	€10 ³
United States	\$13,901 ²		

¹ Valued in year 2000. (Lazzaro 2003)

² Drug costs are from 2006 and all other costs or charges were either inflated to the year 2006 level using consumer price indexes (France, Germany, Italy and Spain) or a health inflation index (UK). The cost of initial treatment over 1 year after initial diagnosis was calculated for all patients diagnosed with a specific stage, not only those treated. UK costs were converted to Euro at an exchange rate of £0.79 = €1, as of August 2008. (Fourcade et al 2010)

³ Valued in year 2009, estimated health-care costs consisted of expenditure on care in the primary, outpatient, emergency, and inpatient settings, and also drugs. Additionally, costs of unpaid care provided by relatives or friends of patients (i.e., informal care), lost earnings after premature death, and costs associated with individuals who temporarily or permanently left employment because of illness were included. (Luengo-Fernandez et al 2013)

Even with variation of the results regarding both the 1st year and year 4-5 costs, these results can be used to estimate the plausible cost and burden level caused by PC. There has also been an increasing interest in evaluating the impact of cancer on employment and thus productivity. Results in Table 1 (Total burden from PC) are supporting the Sanyal et al (2013) estimate that PC is a significant burden on societies.

In Finland, the costs of PC have been mainly studied in the context of other cancers (Mäklin & Rissanen 2006; Kalseth et al 2011; Syöpätautien asiantuntijaryhmä 2014). In total, treatments in cancer care utilize around 4% of the total health care budget. It has been estimated that in 2004 the total cost of managing PC in Finland was €180 Million (M), which was more than double compared to the management of breast cancer (BC) (Mäklin & Rissanen 2006). However, since then there have been other estimates for the burden caused by cancer care, and results have changed over the years, but varied between €750M and €1,500M (for 2020) (Syöpätautien asiantuntijaryhmä 2014). Torkki et al 2017 estimated that the total cost of cancer care in Finland in 2014 was €927 Million.

In an EU country comparison study from 2009, it was estimated that the health care cost of PC was annually €16 per every inhabitant in Finland, which was the third highest share per person after Germany and Luxemburg (Luengo-Fernandez et al 2013). The biggest total direct health care cost (€88M) drivers in PC in Finland were inpatient care (€38M) and medication (€34M). Other costs included primary care €3M, outpatient care €10M, and accident and emergency care €1M. Estimated productivity losses due to PC were €11M, which was mainly driven by mortality (€8M) and, to a lesser extent, morbidity (€3M) (Luengo-Fernandez et al 2013). The cost of informal care was estimated to be €16M annually, and combining both total direct health care cost and productivity losses and informal care, this sums up to €114M as a total cost due to PC in 2009 (Luengo-Fernandez et al 2013). If Finland is assumed to have 47,500 PC patients, this would result in an average of around €2,400 per PC patient.

Spending on pharmaceuticals has emerged as a frequently discussed topic in public debate as new expensive medicines have been developed. Regarding oncology, and more specifically PC medications in Finland, more than 10 new medications have entered the market during the last decade or so (e.g., docetaxel, cabazitaxel, denosumab, abiraterone, radium -223, enzalutamide). The sales of antineoplastic and immunomodulating agents (€423M) grew 11% in 2013, even though the wholesale prices of many reimbursable drugs within this group were lowered by 5%. The sales of antineoplastic agents (€169M) were up by 4%, the sales of endocrine therapy (€29M) by 32% and the sales of immunosuppressants (€170M) by 22%. The sales growth seen in endocrine therapy was mainly attributable to the tripling of the sales of abiraterone (€10M) used in the treatment of PC. The increase seen in the sales of immunosuppressants was also greatly attributable to the growth seen in the sales of new drugs (Finnish Medicines Agency and Social Insurance Institute 2014). In 2015 there were 21,093 patients, who were entitled to special refunds due to their PC. The average cost per patient was €1,674. However, 643 patients were entitled to gain special refunds to abiraterone and enzalutamide, where the average cost per patient was substantial, €28,989 (Finnish Medicines Agency and Social Insurance Institute 2016).

2.2 Health-related Quality of life

Health-related quality of life (HRQoL) is an important and broad concept of patients' experience of health. It reflects the physical, psychological and emotional dimensions of health (Gold et al 1996). It can be used e.g., to describe general wellbeing of a person, or to assess how disease would impact on a person's HRQoL. Information on HRQoL is also vital to be able to make informed choices about treatments for PC, especially since the increased use of PSA testing based screening now exposes more patients to the knowledge of their early PC, when there are multiple treatment alternatives to choose from.

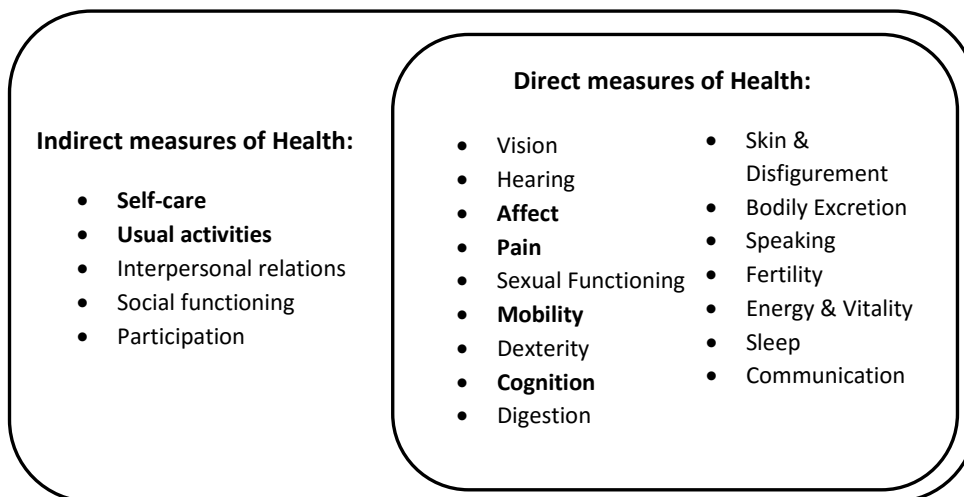
During the last three decades the use of HRQoL instruments has become more popular as a consequence of general acceptance of an approach to describing health states of individuals in terms of multiple domains of health, and in developing self-reporting instruments to seek information regarding these. During the same time period there has been a shift in thinking about health

conditions: the focus has moved from diagnostic descriptions towards understanding health conditions in terms of disabilities, functioning and health states.

In order to measure and report on the health of populations or individuals we need to develop a valid, reliable and comparable way to measure the health status. This requires at least the following: a classification of health state domains, specification of a set of domains necessary and sufficient to describe health states for measurement purposes, specification of what we are measuring in each domain, and a common understanding of what is full health versus exceptional talent in any given domain.

The WHO definition of health notes that health is a multi-dimensional concept (Sadana et al 2000). There are potentially three sets of domains that can be specified in order to describe health and contribute to a health state description: 1) core domains of health that almost all people agree upon as important to the direct measurement of health, 2) additional domains of health that most people agree are direct measures of health, but that might not provide important information additional to the core domains, and 3) domains that are related to health and might serve as good proxy measures of the experience of health (i.e., those that are indirect measures of health). Potential domains in each of these three categories are illustrated in Figure 1, based on an extensive review of existing health state measurement instruments and health measurement literature (Sadana et al 2000).

Figure 1. Different domains of Health.



The items in bold are proposed as the core domains that almost all people agree upon.
Figure 1 is adapted from Sadana et al 2000.

In this dissertation the concept of HRQoL was studied from the following points of view: 1) studied instruments are used in clinical practice, 2) instruments can be used in health economic analysis, 3) to have both generic and disease- specific instruments, 4) instruments are self-administered, widely used, validated and standardised. From health economic analysis point of view, focus was put also on

having generic index based instruments which can be used directly to calculate QALYs for cost-utility analysis.

Following HRQoL instruments were chosen to be used and analysed for this dissertation: disease- (cancer) specific EORTC QLQ C30, and two generic (index) instruments 15D and EQ-5D-3L. All these instruments are widely used and were considered good candidates to study patients' HRQoL in different states of PC. These instruments can be considered to represent 'generic' instruments in terms of not having very deep disease specific questions. Of course, the cancer-specific EORTC QLQ-C30 will have common cancer-related symptoms questions (e.g., fatigue and vomiting) but not specifically PC related questions (e.g., frequent urination, erectile dysfunction) although the generic 15D covers some of these symptoms (e.g., sexual functioning and excretion). Having different types of instruments was also one of the aims: can different types of instrument be used in this setting and will they generate results that are similar or different? Having these 'generic' instruments may lead to a situation that some of disease characteristics (PC-related symptoms) may have been overlooked or not emphasized as much as they deserve (compared to PC-specific instruments), although the idea was more to focus on HRQoL measurement in general. These instruments would allow HRQoL comparison of different diseases in health economic analysis. All studied instruments are also covering more or less extensively the WHO's domains of health.

HRQoL can be assessed in different ways: there are disease-specific, generic and preference- (utility-) based methods. Different levels of problems or dimensions can be described with different disease-specific or generic instruments. Disease-specific instruments are used for studying the most important effects of a given disease on patients' HRQoL. However, they are not suitable for comparison of different health care interventions across different disease entities. Thus, they are useful for providing insights into patients' symptoms and functionality, and are well suited for clinical decision making. Good examples of disease-specific instruments that are widely used to evaluate PC patients HRQoL are the 27-item Functional Assessment of Cancer Therapy (FACT-G) scale (Esper et al 1997), the 12-item prostate cancer-specific tools (FACT-P) scale (Cella et al 1993), the International Prostate Symptoms Score (IPSS) (Barry et al 1992), the UCLA Prostate Cancer Index (UCLA-PCI) (Litvin et al 1998) and the Expanded Prostate Cancer Index Composite (EPIC) (Wei et al 2000). More information regarding disease-specific quality of life instruments can be found from a recent systematic and standardised comparison (Schmidt et al 2014).

The advantage of generic instruments is that they can be used across different patient groups with diverse underlying diseases or disabilities. The generic instruments can be classified into two groups: profile and single index score instruments. The profile instruments measure, depending on the instrument, a broad scale of physical and emotional dimensions. The Short Form 36 (SF-36) (Brazier et al 2002), for instance, generates dimensions such as vitality, emotional role functioning, and social role functioning. The single index instruments provide a single index score usually between 0 and 1, although other scales also exist.

Utilities, preference weights, quality weights, health state values, all these terms are used interchangeably, can be elicited for single index score instruments by direct or indirect valuation methods. The aim of the health state valuation is to establish population preferences or so called quality weights for the different health states defined by the health state descriptive system. Typically, in the direct and holistic approach, the health states to be valued are described in written

form to those from whom the valuations are elicited (the respondents) who must imagine themselves in those hypothetical states. Using the indirect approach, the valuation is divided into parts or stages and the final HRQoL scores for different health states are aggregated from the results of those stages.

The most used application using utilities is the quality-adjusted life-year (QALY), which takes into account both the quantity and quality of life generated by a health care intervention. The basic idea is very simple: a year of life lived in perfect health is worth one QALY, and a year lived in a state of less than this perfect health is worth less than one QALY. A QALY places a weight (utility, preference weight, quality weight, health state value) on time in different health states typically ranging from 0 (=dead) to 1 (=perfect health). In order to assess the exact QALY value, the utility value associated with a given state of health needs to be multiplied with the time spent in each state. The QALYs gained provides a common transferable currency for measuring the extent of health gain that results from health care interventions, and when combined with the costs associated with the intervention, the relative worth of the intervention from an economic perspective.

The most commonly applied method of constructing QALYs is based on an individual-based approach of value measurement, and this can be considered being consistent with the principle of consumer sovereignty, the keystone of welfare economics (Weinstein et al 2009). Individual health preferences are measured with techniques such as the standard gamble (SG), time-trade-off (TTO), and visual analogue scale (VAS) (or rating scale). In TTO respondents are asked to choose between remaining in a state of certain health for a period of time, or being restored to perfect health, but with having a shorter life expectancy. In SG the choice is between remaining in a state of certain health for a period of time, or choosing a medical intervention which has a chance of either restoring them to perfect health, or killing them with a certain probability. In VAS, however, persons are asked to rate a state of health on a scale from 0 to 100, with 0 representing being dead and 100 representing perfect health. This method has the advantage of being probably the easiest to ask.

The SG is based on well-defined, widely accepted axioms of consistency of preferences under uncertainty such as transitivity, independence, and continuity. The TTO has a unique conceptual relationship to QALYs, because it tries to measure explicitly a trade-off between the time in an impaired health state relative to healthy quality-adjusted time. The TTO is also theoretically equivalent to the SG under the conditions in which QALYs are appropriate as a utility, which include risk neutrality with respect to longevity. Rating scales (including VAS) have sometimes been considered theoretically inferior to SG or TTO (Weinstein et al 2009), but there are problems, both theoretical and empirical, with alternative methods as well (Parkin & Devlin 2006). Parkin & Devlin (2006) recommend that the selection of the appropriate valuation method should be based on empirical performance, and in this the VAS has important advantages. They conclude that there are strong grounds for disputing the consensus view against the VAS and challenge those who hold it to deploy more convincing arguments and evidence in favour of alternative methods.

With multiattribute utility instruments (e.g., EQ-5D, HUI2, HUI3, SF-6D, QWB, 15D) the health states are valued as a matrix of combinations of health domains (or attributes) which are associated with the particular instrument. For instance the 15D has 5¹⁵ health states which are defined by selecting one of 5 levels of health within each of the 15 dimensions. Respondents classify themselves into one

of the cells in these matrices. Each of the cells comes with the score that has been previously obtained by a survey of respondents of the general public.

Figure 2 presents a situation where intervention B provides a consistently greater area under the time curve than intervention A and the shaded area between the curves represents the QALY gain from intervention B in comparison to intervention A. Intervention A QALYs can be calculated as follows: $k_1V_1 + k_2V_2 + k_3V_3 = \text{QALY}_A$, and QALYs for Intervention B: $k_4V_4 + k_5V_5 + k_6V_6 + k_7V_7 = \text{QALY}_B$. QALYs gained for health economic analysis is difference between the interventions: $\text{QALY}_B - \text{QALY}_A = \text{QALYs gained}$.

Figure 2. QALYs gained from intervention A in comparison to intervention B.

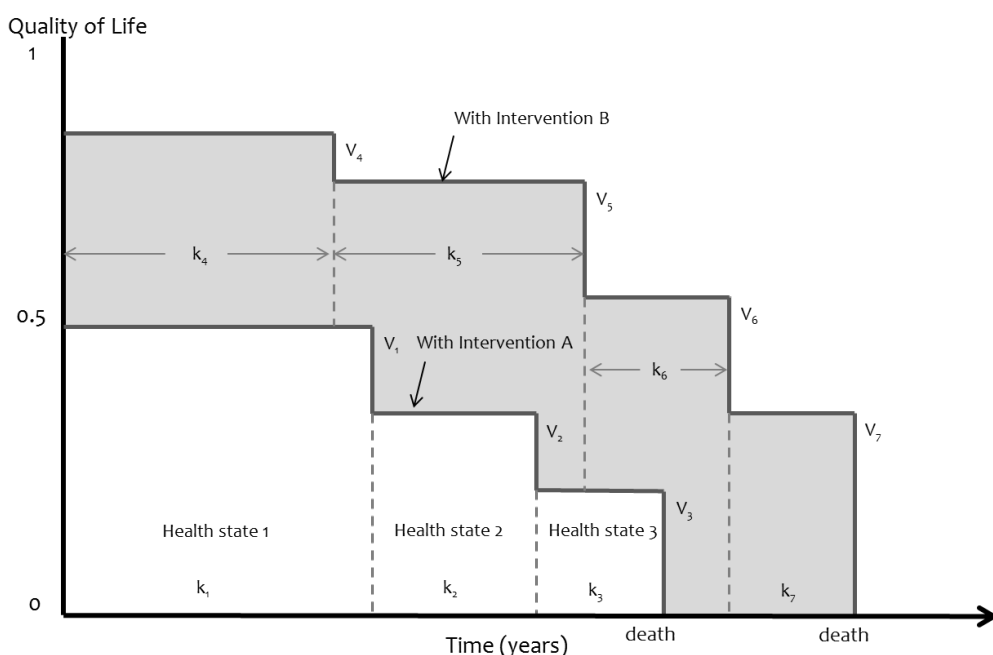


Figure 2 is adapted from Sintonen (2007).

HRQoL has been extensively studied in PC and over 2000 publications were found to be related to HRQoL in PC since 2002 (Torvinen et al 2016b). From a health economic point of view it is striking that only a fraction of these studies used preference-based index score instruments and thus reported data that can be used for QALY calculations. The choice of the utility instrument has proven to have a large impact on the results of cost-utility studies (Stavem 1999; Brazier et al 2004). This is impacted by the differences in the health descriptive systems and the methods used to value the health states defined by the descriptive system. However, there is no consensus regarding a gold standard HRQoL instrument.

In a Finnish study, Kuivalainen (2004) studied PC patients' HRQoL before and during the first year after treatment. She used the disease-specific instruments EORTC QLQ-C30 and EORTC Pr25, and the generic instruments 15D and EQ-5D. Pain was found to be related to reduction in HRQoL during the first four months after treatment, and was related to patients' reported social function, role function and insomnia. Urinary disorders were worse during four months after treatment, and they impair HRQoL, especially in terms of insomnia and fatigue. In general, 15D and EORTC correlated significantly with each other and both instruments were considered appropriate.

2.3 Cost methods

Costing typically involves identifying, measuring and valuing all resource utilization that occur as a certain health care intervention is carried out in order to gain health effect (Brouwer et al 2001). Unfortunately it is not an easy exercise to solve the puzzle related finding straightforward method of valuation when determine the value of the cost items. For instance societal costs of services provided or patient time are not easy to value. Notably health care market is lacking perfect market conditions, and prices cannot be considered to reflect opportunity costs, and other methods like shadow prices needs be considered. In order to make robust assessment of an intervention, all costs and consequences needs to be examined regardless of who bears the burden or where they occur in society.

Figure 3. Categories of changes in resource use.

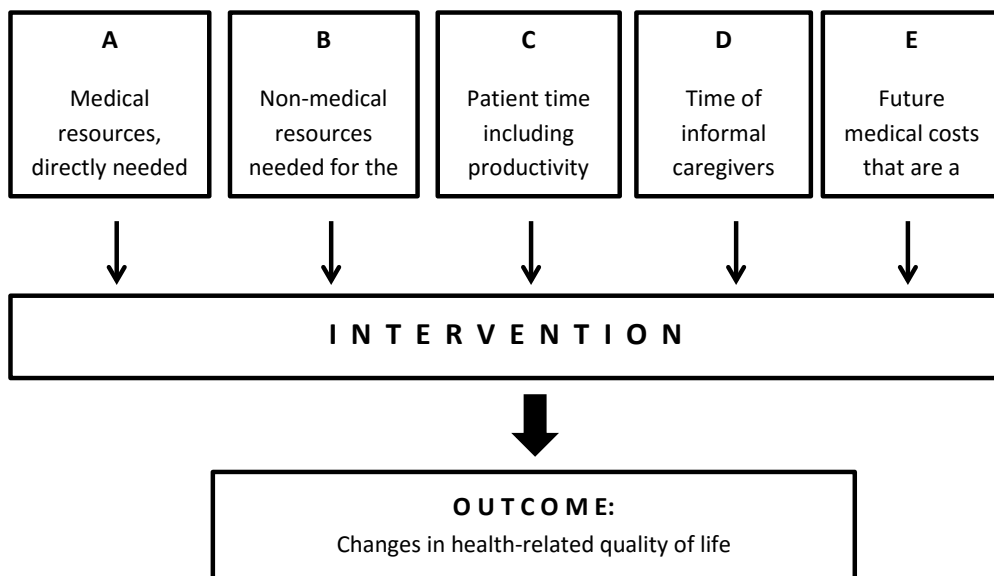


Figure 3 is adapted from Brouwer et al (2001).

It is relatively rare that in cost of illness (COI) studies all the costs related to disease have been taken into consideration (Mäklin & Rissanen 2006). Similarly health economic evaluations are in practice using mainly direct medical and healthcare costs. These are generally easier to measure, but neglecting indirect costs may lead to an underestimation of the true cost of a disease. Particularly, disregarding productivity losses may result in an undervaluation of the disease burden. Informal care provided by family members or relatives and friends is an important element of care for many cancer patients and, therefore, cost of informal care is recommended to be included in economic evaluations.

Direct health care costs

Direct health care costs usually consist of *specialist care/hospital* costs including inpatient episodes and outpatient visits to secondary health care. Direct health care costs should also include *primary health care* that can include information on general practitioner and nurse visits, home hospice care and primary care hospitalisation. Also data concerning the use of *private health* services should be included. The cost of *Medicines* (outpatient/inpatient) is usually one of the easiest and most precise metrics to collect due to the controlled systems regarding reimbursement and dispensing of medicines.

Direct non-health care costs

There are also directly measurable costs which can be linked to utilization of the health care services but are still to be considered direct non-health care costs. For instance *Cost of travelling* to the facilities where treatment is given is sometimes directly measurable, but usually some level of estimations and assumptions are needed to calculate these.

Productivity costs

From an economic point of view, cancer-related productivity losses emanate from the value of production lost due to morbidity and premature mortality. Traditionally, morbidity costs consist of the value of production lost due to short-term cancer-related work absences, in addition to permanent absence from the workforce before conventional retirement age. Premature mortality costs comprise the value of production lost due cancer-related death before conventional retirement age. Although it is easy to delineate cost components that are required for the analysis, the appropriate method to measure and value the productivity costs associated with disease has been an area of considerable debate (Koopmanschap et al 1995; Johanneson & Karlsson 1997; Liljas 1998; Zhang et al 2011).

In the cancer setting, the most frequently used method to estimate productivity losses is the human capital approach (HCA) (Tinghög et al 2005; Lidgren et al 2007; Bradley et al 2008). HCA takes the societal perspective and counts any hour not worked as an hour lost. By contrast, the other method used, friction cost approach (FCA), takes the employer's perspective and only counts as lost those hours not worked until another employee takes over the patient's work.

There are issues in using either of these methods such as higher earning potential valued over the low income potential (e.g. young/old/race/educational level etc.). Both methods may also over-estimate real production losses and they assume that gross earnings reflect real productivity.

A noted advantage for the HCA is that it can be judged to be credible as it is founded on economic theory, although there is also criticism due to the same reason; the neoclassical assumptions underpinning the methods are unrealistic. For instance, it assumes full productivity and employment, and that labour markets are competitive, and that workplace productivity is assumed to be paid for by employers with a wage that is directly proportionate to the employee's contributions to the firm (Tranmer et al 2005). Nevertheless, the HCA is easy to apply and intuitive from an employer perspective.

FCA values production lost due to disease depending on the time-span an organization needs to restore the initial production level (i.e., cost of replacing a reduced or disabled working capacity). This would require data on whether the work can be completed by an employee with reduced or disabled working capacity, frequency of the friction period, and knowledge of the economic cost of lost production. This might have an advantage such as a more accurate measure of lost productivity, but requires assumptions that are practically impossible in many jobs, such as it assumes perfect market for supply of workers (van den Hout 2010).

Hanly et al. (2012) found in their study, using PC and breast cancer (BC), that result may differ substantially between the approaches (i.e., HCA vs FCA). For BC, the FCA total productivity cost estimate amounted to 4.2% of the equivalent HCA estimate, whereas in PC, it was 7.5%. In PC, this would result in total productivity losses of €109,154 (HCA) and €8,205 (FCA) per patient at the 2008 price level. The reason for this can be explained by different economic perspectives (i.e., society [HCA] vs. employer [FCA]) and time frames associated with approaches (until end of working life; long-term [HCA] vs. until worker's efforts are replaced; short-term [FCA]). Nevertheless, so far there is no consensus on this topic and the human capital approach remains the most commonly used method (Hanly et al 2012).

Informal care

Informal care can be defined as care that patients receive free of charge from family members and/or friends. Informal care can make up a significant part of the total care provided to care recipients with chronic or terminal diseases (Norton 2000). Regardless of this, the costs and effects of informal care are often ignored in economic evaluations (Stone et al 2000).

Informal care costs have been less studied compared to productivity costs, but for instance Buckner & Yeandle (2011) reported that alone in the UK the informal care economy is substantial, with almost 6 million carers in the UK recorded in the 2001 census. For valuation, it is important to recognize that informal care is a non-market or quasi-market of services supplied by carers who are often unpaid, or who receive only nominal payments or state benefits that do not reflect the true cost or benefits of the care (Weatherly et al 2014). Usually informal care is measured by time spent caring, but it is difficult to distinguish informal care activities from usual household activities that would be undertaken anyway. The time spent on caring can be assigned a monetary value by using a range of techniques: revealed preference using the opportunity cost, proxy good or wellbeing valuation

method; or stated preference using discrete choice experiments or contingent valuation (van den Berg 2004; Koopmanschap et al 2008; Goodrich et al 2012).

2.4 Economic evaluation

Health economic evaluations of new medicines or other technologies have become common practice when they are introduced to health care systems. This assessment can take different forms depending on the situation. However, the most frequently used methods are cost-minimization analysis (CMA), cost-benefit analysis (CBA), cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) (Drummond et al 2005). In CMA the effectiveness of the comparators in question must be proven to be equivalent. The preferred 'cost-effective' alternative is simply the one which costs less (same outcomes). In CBA costs and benefits are both valued in monetary terms. CEA measures outcomes in 'natural units', such as a change in blood pressure (mmHg), symptom free days, or life years gained. Finally, CUA measures outcomes in a composite metric of both length and quality of life usually expressed as the quality-adjusted life year (QALY) gained.

Table 2. Different types of economic evaluation methods.

Method of Analysis	Cost Measurement	Outcome Measurement
Cost-minimization Analysis (CMA)	Monetary (€)	Equivalence demonstrated in comparative groups
Cost-effectiveness Analysis (CEA)	Monetary (€)	Single 'natural' unit outcome
Cost-utility Analysis (CUA)	Monetary (€)	Multiple outcomes – life of years, adjusted life years (QALYs) gained
Cost-benefit Analysis (CBA)	Monetary (€)	Monetary (€)

Table 2. Adapted from Drummond et al (2006).

A cost of illness (COI) study is also sometimes classified as an economic evaluation. Yet it is not a true economic evaluation as it does not compare the costs and outcomes of alternative courses of action. Instead, it attempts to measure all the costs associated with a particular disease or health condition. COI studies are, however, important as they try to describe the economic burden of a disease to society. These typically include direct costs, indirect costs (the value of lost productivity from time off work or diminished ability to work due to illness), and informal care (amount of informal care received free of charge from family and friends) costs. Sometimes also intangible costs (the 'disvalue' to an individual caused by pain and suffering) have been evaluated.

Incremental cost-effectiveness

The use of QALYs as an outcome in health economic evaluations has become popular during the last three decades. Simply, if there are two interventions to compare, a decision needs to be taken on

which one is the better option. The decision can be based on which option is less costly or provides better value (e.g., QALYs gained). If one alternative is both less costly and provides better value (outcomes), it is a dominant option (strong/strict dominance). In weak (or extended) dominance there is another option that is more effective and more costly, but provides better value for money (lower incremental cost-effectiveness ratio, ICER). Also, with weak dominance, two options can be selected that, when combined, provide strong dominance regarding a third alternative. This refers to the ratio of the difference in costs (incremental costs) divided by the difference in outcomes (incremental effect) between two alternative interventions. If there are more than two alternatives, interventions are compared on a systematic pair-wise basis using their ICERs. The results of a CEA or CUA should be reported in terms of ICER (or incremental cost-utility ratio, ICUR). In the simple form this means that the cost difference between the interventions (old and new) is divided by the difference in HRQoL or QALYs between the interventions as a measure of effectiveness (e.g., cost/QALY).

$$ICER = \frac{\Delta Costs}{\Delta HRQoL}$$

Many times, in a real world situation, a new treatment is more effective, but also more costly compared to standard of care (old therapy). In that case the final decision regarding cost-effectiveness will depend on the society's willingness to pay (WTP) for the extra effectiveness (Briggs 2001). WTP corresponds to the value that the society is willing to invest in an additional health unit gained, e.g., QALY. The WTP threshold ultimately determines whether the new intervention is regarded as being cost-effective or not. This approach has been criticized for not being fair and transparent in all the situations, but evidently fixed thresholds are widely used globally (Grosse 2008). The maximum threshold varies between countries, for example the National Institute for Clinical and Care Excellence (NICE) recommends £30,000, or higher for end-of-life care, and for instance in the Netherlands around €20,000 (Health Council 2007) has been mentioned unofficially. Many countries have used the WHO recommended approach that an intervention is highly cost-effective if the incremental cost-effectiveness ratio (ICER) is below the per capita gross domestic product (GDP) and cost-effective if it is below 1-3 times GDP (Marseille et al 2015). In Finland the decision-makers have not specified an explicit range of threshold values for a cost per QALY gained what should be considered cost-effective. Regardless of the debate concerning the right value, it has been argued that the threshold lacks an empirical basis and by using only ICER and WTP, equity and fairness could be disregarded (Rawlings & Culyer 2004). The latest movement in this debate is that Spain announced in early 2017 that they are walking away from using QALYs in their HTA after the US and Germany, who did the same earlier. They are considering that QALYs are not methodologically and ethically robust enough (Arganda 2017).

Health economic evaluations: case example of PC

Two most used frameworks in economic evaluations are decision trees and state transition models (Karnon 2003, Brennan et al 2006). For illustration on how resource use/cost and HRQoL data can be used in PC evaluations, a dummy PC Markov model illustration was developed. Markov models have

become a frequently used method in economic evaluations, since they allow researchers to construct flexible applications to reflect disease progression using constant, time-dependent, and discrete processes (Briggs & Sculpher 1998). These can describe the natural course of diseases (e.g., PC). These transitions between ‘health’ states can be graphically represented using a state transition diagram shown in Figure 4. Transitions between specified ‘health’ states will occur until all members of a hypothetical cohort are moved to the “Death” state.

Figure 4. Markov model in PC illustrated as a state transition diagram.

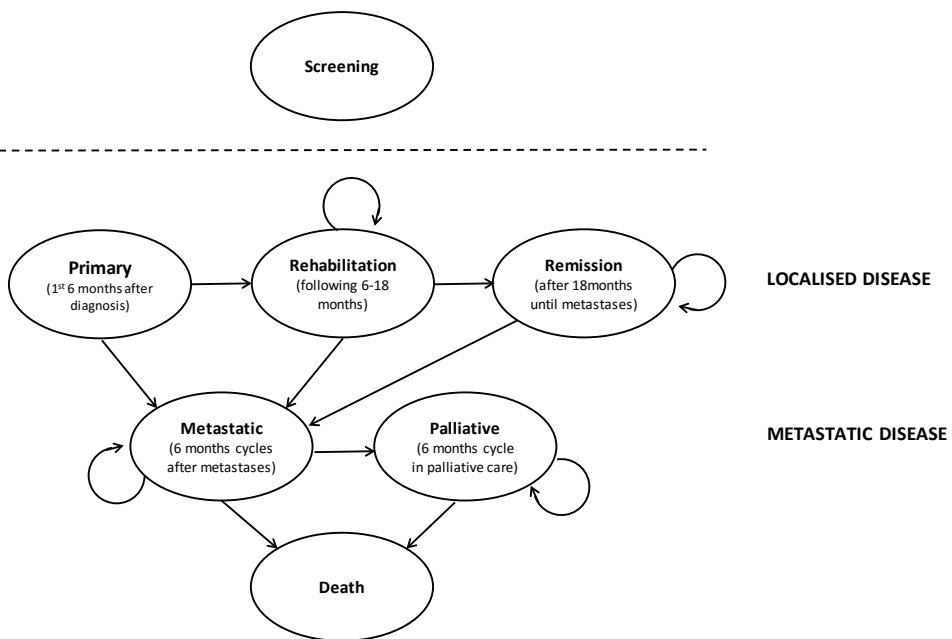


Figure 4. Circles correspond to health states and arrows correspond to possible transitions with associated probabilities from one health state to another.

Markov models can have constant probabilities of transitions between states or they may be allowed to vary according to another model variable. Two fundamental assumptions behind Markov models are that the probability of moving out of a health state is not dependent on the health states that a patient may have experienced previously (no memory) and that the health states are mutually exclusive (one person only in one point in time or place). In the PC model presented in Figure 2 that would mean that a patient would start from *Primary* state, stay in that state for 6 months (6 months cycle) and after that move to *Rehabilitation* state or to *Metastatic* state if metastases are found. Again after 6 months in the *Rehabilitation* or *Metastatic* states the patient will either stay in that state or move on to another state depending on state transition probabilities. The model would be run until the end of cycles or as long as all the patients end up in the state “*Death*”, where it is not possible to move anywhere. This model structure could be used to evaluate the impact of screening on PC, and the impact of different interventions (e.g., new medicines/operations) introduced in

different states of the disease. In this thesis baseline HRQoL and cost data have been evaluated for all these states (excluding screening). In addition to that, the state dependent transition probabilities are needed for the analysis. In the simplest case costs and HRQoL could be assumed to be similar in two treatments to be evaluated, and the only difference between the treatments would be that in the transition probabilities between states (i.e., disease progression probabilities). An example of this is a new treatment for localised disease that reduces the probability of moving to metastatic disease state. Assuming that there would not be any side effects and HRQoL would remain at a similar level and the only things that would change are the cost of the new intervention and improved probability of not moving to metastatic disease, this model structure could be used as described.

3. STRUCTURE AND AIMS OF THE THESIS

The motivation for the empirical study was the rising importance of PC with aging of the population and the improved screening and treatment options. Evidence on both cost/resource utilization and HRQoL in PC is scarce but such data are needed to perform CUAs throughout the whole treatment path starting from screening and early diagnosis all the way to the end-of-life treatment. The aim of the empirical studies is to generate data that can be used in CUAs assessing various treatment options of PC. Another reason for doing such a study was to gain better understanding for the reasons behind resource utilisation and costs, and to identify factors that impact HRQoL in different states of PC. By understanding these, it may be possible to emphasize the right things in the treatment path and to proactively help patients to undergo treatments. Results are also supporting every day clinical decisions on what are the factors potentially influencing patients' experienced HRQoL in different states of PC.

Specific aims for this study were:

- 1) to review systematically evidence on the usage of generic, validated HRQoL instruments that can be used to calculate QALYs, and consequently are useable directly for health economic evaluations in PC;
- 2) to measure the PC patients' HRQoL, by using different instruments, in different states of the disease; to compare the HRQoL of patients to that of the age- and gender-standardised general population; to compare the results of different instruments and to look for factors influencing HRQoL, to compare can they be used interchangeably in health economic analyses;
- 3) to estimate the real-life costs in different states of PC. Costs include direct healthcare or medical costs, productivity costs and costs of informal care.

4. MATERIALS AND METHODS

4.1 Patient population and study design

The patient data were collected in the Helsinki and Uusimaa Hospital District that provides specialist medical care for the approximately 1.5 million inhabitants of Southern Finland. The study was a cross-sectional observational survey approved by the local Ethics Committee (registration number 207/13/03/02/2008). PC data were collected as a part of a larger study, where similar data were collected also for colorectal (CRC) and breast cancer (BC). Patients were enrolled between September 2009 and December 2010.

Patients were enrolled in a cross sectional setting and all patients over 18 years of age and diagnosed with PC were eligible for the study. A research nurse identified patients from hospital records by date of diagnosis based on the tenth version of the International Statistical Classification of Diseases and Related Health Problems (ICD-10; PC code C61) as primary or secondary diagnosis. The nurse mailed questionnaires to those identified patients who consented to participate. Recently diagnosed patients and those receiving only palliative care were enrolled when visiting the hospital. Non-respondents received one reminder letter. Clinical background information regarding patients' disease stage and treatments administered within the last three months were collected from hospital records.

Patients were divided into five mutually exclusive pre-selected groups based on disease state: *Primary* (local disease, first six months after diagnosis), *Rehabilitation* (local disease, 0.5 – 1.5 years after diagnosis or recurrence), *Remission* (local disease, more than 1.5 years after diagnosis), *Metastatic* (after detection of metastases) and *Palliative care*. *Palliative care* patients were defined as patients having metastatic disease and receiving palliative treatments only (defined by no chemotherapy or radiotherapy), and patients who died due to cancer within six months of responding to the questionnaire, irrespective of the treatment given. These groups were formed when the nurse made the initial search to the hospital records based on time of the diagnosis. Some patients were moved from the local disease groups to the metastatic or palliative group if the disease had progressed.

Unfortunately it was not possible to perform non-responders analysis. There were no access to patient records when patient did not want to participate and therefore consent to have access to patient records were not permitted. Only analysis on patients' age was possible and there was no difference between responders and non-responders (69.4 vs 68.2, respectively).

Patients' background information was collected simultaneously with questionnaires, which covered details regarding marital status, education, occupational status, treatments received outside hospital, and informal care. Utility scores were compared to scores from the general population obtained in the representative Finnish Health 2000 Health Examination Survey (Aromaa & Koskinen 2004). The set of questionnaires covered a relatively wide range of topics over 10 pages with a total of 76 mostly multiple-choice questions (Appendix 1).

4.2 HRQoL Instruments

Two generic self-administered HRQoL instruments were used: the 15D and the EQ-5D-3L (with VAS), as well as the cancer-specific EORTC QLQ-C30 questionnaire. All instruments are widely used, validated, and standardised.

15D

The development of the 15D started almost 40 years ago with the idea of combining the advantages of a profile and a preference-based measure. The conceptual basis for the health state descriptive system was based on the definition of health by the World Health Organisation (WHO), and the first 15 dimensional 15D with a health state descriptive system came out 1986. Based on the feedback received, this version included three new dimensions (depression, distress and pain) in addition to the 12 dimensions of the earlier released instrument (Sintonen 1981; Sintonen & Pekurinen 1989; Sintonen & Pekurinen 1993). The suitability of this instrument regarding its ability to reflect HRQoL was tested among nearly 3,000 individuals and after revisions an updated version was launched in 1992. In this version, the ability to work and social participation were combined into one dimension, labelled “usual activities” and a new dimension on sexual activity was added. In addition, all dimensions were changed to five-level scales in order to increase sensitivity.

The present 15D is a generic instrument with 15 dimensions (*mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity*). Each of the dimensions has 5 answering levels (1=best level; 5=the worse level) of which a person chooses the one that best describes his/her state of health at that moment. The 15D can result in 5¹⁵ possible combinations of describing different health states.

The valuation (indirect) of the 15D is based on an application of the multi-attribute utility theory. A set of utility or preference weights, acquired from representative samples of the general public through a 3-stage valuation procedure, is used in an additive aggregation formula to generate the utility score, i.e., the 15D score (single index) over all the dimensions. In short, during the first stage, relative importance weights were elicited from the top levels of the 15 dimensions. At the second stage, importance weights were elicited from the lowest levels (5) of the dimensions. The valuation procedure was completed using a 0–100 ratio scale (VAS scale) (100=the most important, 0=not important at all). The ratio scale nature of the valuation task was emphasized by placing nine arrows to the right-hand side of the 0–100 scale with a text explaining how the number pointed by an arrow should be interpreted over the range of the scale. For example, if an arrow is pointing to 90, it should be interpreted as 90% as important as the most important attribute. The importance weights for the intermediate levels were extrapolated linearly from the weights of the extreme ends in relation to the distance between level values, which were elicited for each dimension during the third stage. On top of the five levels, the states “unconscious” and “dead” were valued on for every dimension. The preference weight for each level was calculated by multiplying the level weight by the importance weight for the dimension. The most important dimensions for good HRQoL are mental function (i.e.,

to be able to think clearly and logically), to be able to breathe normally and, to be able to perform usual activities (such as work, leisure and hobbies) normally.

The 15D index score ranges from 0 (=being dead) to 1 (=full health). The minimal clinically important difference (MID) in the 15D has been estimated at 0.015 (Alanne et al 2015). The 15D is available in more than 30 languages and has been widely used in many different diseases. Based on the 15D, there is also available the 16D for adolescents aged 12-15 years and the 17D for children aged 8-11.

EQ-5D-3L

The EQ-5D-3L was initially developed simultaneously in Dutch, English, Finnish, Norwegian and Swedish by The EuroQol Group. The EuroQol Group was established 1987 and it comprised a network of international, multilingual, multidisciplinary researchers, originally from seven centres in England, Finland, the Netherlands, Norway and Sweden (Euroqol 2017). The main purpose of the Group was to explore, whether the health state valuations are similar across a number of European countries. To this end a simple health state descriptive system (questionnaire) was created, a set of standard health states was derived from the system, and a way of valuing these states in a postal survey (using a VAS “thermometer”) of a representative population sample drawn in a standardised way was devised.

The first health state descriptive system of the EQ-5D-3L was developed through a conceptual process on the basis of the available HRQoL instruments. Reviewed instruments represented both generic and profile instruments (e.g., the Quality of Well-Being Scale, the Rosser Index, and the 15D) (Coast 1992; Coons et al 2000; Sintonen 2001), whereas some were simple profile instruments (e.g., the Sickness Impact Profile, the Nottingham Health Profile and the Health Measurement Questionnaire) (Cole et al 1994).

The first version consisted of six dimensions (*mobility, self-care, main activity, social relationship, pain and mood*) with two to three levels on each dimension. The levels of the dimensions were on a scale (The EurQol Group 1990). On the basis of experiences and experiments, a new version was ratified in 1991. The dimension *social relationships* was excluded, and all remaining five dimensions were changed to include three levels (84). The names of dimensions were also partly changed and are now *mobility, selfcare, usual activities, pain or discomfort, and anxiety or depression* (The EuroQol Group 1990; Brooks 1996). The respondent chooses from these three levels (no problems, some problems, extreme problems) based on their perception of health today.

Originally the Group agreed to use a VAS “thermometer” to elicit valuations for generating a single-index score for the health states defined by the EQ-5D descriptive system. In the VAS valuation system, the end points of the scale are the best imaginable (=100) and the worst imaginable (=0) health state. In the VAS valuation process, respondents draw a line from boxes describing different, earlier defined health states on the scale (“thermometer”) to indicate how good or bad the status is.

The main conclusion from the valuation studies carried out to meet the Groups original purpose was that “there appears to be a considerable degree of agreement between health state valuations in studies from several European countries, with the exception of Spain” (Sintonen et al. 2003). The EQ-

5D-3L thus created was not intended to be used as a stand-alone instrument, but to complement other HRQoL measures and to facilitate the collection of a common data set for reference purposes (Brooks 1996).

The original idea of not regarding EQ-5D-3L as a stand-alone instrument was abandoned, when the English participants, primarily from the University of York, decided to carry out an extensive valuation study (so called MVH study) using the time trade-off (TTO) valuation method. In the TTO method, the respondents choose between two alternatives: x years in full health or a previously defined number of years (e.g., 10) in the health state being valued, i.e., how much of the lifetime the respondent is willing to sacrifice in order to achieve a higher quality of life. In the MVH study 43 of the 243 possible health states were valued by 3,337 respondents of the general UK population. Each respondent valued 11 different health states varying from very mild to severe health states. In addition to perfect and worst possible health state, immediate death and unconsciousness were valued. The respondents completed the health states valuation differently for health states considered better and worse than death (Dolan 1997). The valuations for these 43 health states were used to create a regression model to interpolate an index score for the rest of health states. The scale of the index score is -0.594 to 1 (with the UK TTO tariff), where 1 indicates full health and 0 represents death. The EQ-5D-3L tariff varies between countries — e.g., in the United States, the lowest utility score in the original D1 tariff is -0.102, while in Spain, the lowest is -0.654 (Heijink et al 2011). All of these tariffs have been based on mean TTO valuations. However, a new tariff (-0.81 to 1) based on median TTO valuation has been recommended for use in the United States (Shaw et al 2013). The different scale lengths achieve that the results of applications from these countries are not comparable. We used the UK TTO tariff and in addition we report the scores of patients' global assessments of their health status using the above mentioned VAS "thermometer".

In a comparison, the TTO produced higher utility weights compared to VAS in mild and moderate health states and considerably lower utility weights in severe health states (Brazier et al 1999). For the QALY calculations and cost-utility analyses, it has been recommended that the EQ-5D scores defined by the TTO method should be used (Rabin & de Charro 2011).

The EuroQol Group has not estimated MID for the EQ-5D-3L, however, it has been investigated by using anchor- and distribution-based methods. Depending on the patient group, the anchor-based MID varied from -0.011 to 0.139 and the distribution-based MID ranged from 0.11 to 0.17. For the entire patient population, the mean MID was 0.074 and the median MID 0.081 when estimated using the anchor-based method (Walters & Brazier 2005). For cancer patients, by using same the methods, MID has been estimated to vary from 0.08 to 0.10 (Pickard et al 2007). The EQ-5D-3L has certain characteristics that may hinder the proper evaluation of MID, such as a high ceiling effect (i.e., many patients reach a score of 1 = perfect health), no scores between 0.88 and 1.00, and non-normal and discontinuous distribution of the scores divided into two distinct groups (Saarni et al 2006; Vainiola et al 2010; Parkin et al 2016).

Comparison of the generic HRQoL instruments

There has been increasing interest in which HRQoL instrument should be used. The instruments can be characterised and compared in terms of several aspects. Probably the most important feature is the sensitivity of an instrument. This can be evaluated from two perspectives; firstly, ability to distinguish differences between individuals and groups in different health states cross-sectionally (discriminatory power), and secondly, ability to detect changes in individuals or groups over time (responsiveness to change in health status). Discriminatory power can be evaluated by the ceiling and floor effects. Furthermore, the properties of the distribution of the scores—e.g., skewness and peakedness—can reveal something about the discriminatory power (Sintonen 1994). The ceiling and floor effect and skewness can also give some hints about the instrument's responsiveness to change.

The EQ-5D and the 15D have been compared among patient groups in multiple diseases, and in general, the mean utility scores have been higher for the 15D than for the EQ-5D with the differences tending to be larger when the utility values are low. The 15D has been shown to be more sensitive in detecting change in HRQoL and in discriminating different health states than the EQ-5D (Saarni et al 2006; Kontomodipoulos et al 2012). Although various instruments are available to measure HRQoL in PC, evidence does not indicate whether it is preferable to use generic or disease-specific instruments individually, or in combination. As there is a debate regarding the use of disease-specific versus generic instruments for assessing HRQoL in PC, the HRQoL results obtained with the cancer-specific EORTC QLQ-C30 instrument were also evaluated in this study.

EORTC QLQ-C30

The cancer-specific EORTC QLQ-C30, developed by the European Organisation for Research and Treatment of Cancer (EORTC, founded 1968), assesses the quality of life of cancer patients. It has been translated and validated into 81 languages and used in more than 3,000 studies worldwide. A first generation of the EORTC instrument came out 1987 (EORTC QLQ-C36) (Aronson et al 1991). The EORTC QLQ-C30 version 3.0 is the most recent version. It came out in December 1997 and should be used for all new studies.

The cancer-specific EORTC QLQ-C30 has a question on a global health status and yields five functioning scales (physical, role, social, emotional, and cognitive functions). Fatigue, nausea/vomiting and pain are presented on their own scales, as are six single symptom items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). The EORTC produces symptom and functioning profiles, but not utility values. EORTC QLQ-C30 scoring is straightforward and each of the multi-item scales includes a different set of items. All of the scales and single-item measures range in score from 0 to 100, where a high scale score represent a higher response level (e.g., higher level of functioning). In practice, the first step in scoring is to estimate the average of the item that contributes to the scale (i.e., raw score) and the next step is to use linear transformation to standardise the raw score so that the score ranges between 0 and 100. (Aronson et al 1993; Fayers et al 2001)

The questionnaire has a 1-week time frame (i.e., “during last week”) and uses a four-point response format (“not at all,” “a little,” “quite a bit,” and “very much”), with the exception of the global Health Status scale, which has a seven-point scale. For the functioning and the QL scales, a higher

score indicates better health. For the symptoms scales, a higher score indicates a higher level of symptom burden.

4.3 Literature review on HRQoL (IV)

The objective of the systematic literature review was to identify and qualitatively describe published studies that collected PC patients' HRQoL estimates by using validated generic instruments which can be used to estimate QALYs.

Literature Search

Computerized literature searches were performed without language restrictions using *prostate cancer* and *quality-of-life* as key words according to Medical Subject Heading (MeSH) terminology. Systematic literature searches were conducted on March 16th, 2013 for the years 2002-2013 and on June 18th 2015 for the years 2013-15 from the Medline, Cochrane Library, PsycINFO, and CINAHL databases. Furthermore, the most recent, not yet indexed publications were manually searched among the Pubmed in Process references. The searches were restricted to meta-analyses, systematic reviews, randomized controlled trials, and observational studies. Congress abstracts were not included, but systematic reviews and meta-analysis were included for manual double check that all the relevant publications were covered. The results in Medline were filtered with the filters developed by SIGN (Scottish Intercollegiate Guidelines Network). In addition, bibliographies of potential articles that, e.g., included HRQoL/utility data as inputs of cost-effectiveness analyses were reviewed manually by the researchers.

Inclusion criteria

Initial screening of the identified articles was based on their abstracts, which were reviewed independently by at least two of the researchers and selection of relevant articles was agreed on in discussion between the reviewers. When an abstract did not give sufficiently precise information about the study, or such information was not available at all, the full article was obtained for further review.

Full-text articles obtained for closer evaluation were read independently by at least two of the researchers. Included were those articles in which HRQoL data were collected from PC patients, results were reported as single index utility scores, and validated HRQoL instruments were used (either direct valuation using TTO, SG, VAS, RS or indirect valuation by 15D, EQ-5D, SF-6D, HUI, AQoL, QWB, Rosser-Kind).

4.4 Costs (III)

Costs were estimated as incremental costs due to PC for a six-month period and they included direct health care costs, productivity costs and costs of informal care. Resource use and cost data, irrespective of who the payer was, were retrieved from various registries in the Helsinki area in Finland. In addition, patients answered background questions concerning informal care, work capacity and educational status. Patients were divided into groups as explained earlier.

For every study patient, two control subjects were extracted from the Social Insurance Institution's (SII) electronic records. The control group subjects were standardised for age, gender and place of residence. Costs other than those incurred by specialist care were compared against a control group and reported as incremental costs related to PC for a six-month period. The sample extracted from SII registries covered outpatient medication, sickness allowances and use of private health care. All costs are presented at the 2010 price level.

Direct health care costs

Specialist care. Specialist care data include inpatient episodes and outpatient visits to secondary health care. These retrospective data also included inpatient medicines. All secondary care visits that were not deemed, by an experienced clinician, to be related to PC treatment were thus excluded. All the data, including cost data, came from the hospital's electronic records, and can be considered comprehensive. Costs of travel to treatment were available from the SII records when they exceeded the maximum co-payment for the patient (€14).

Primary health care. Primary health care in Finland is funded and organised by municipalities. Primary health care services are available for all residents in the municipality and services are free for patients with the exception of some user fees. Primary care data were collected from the three largest cities in the catchment area of the hospital, Helsinki, Espoo and Vantaa, covering more than 80% of study patients. The primary care data included information on general practitioner and nurse visits, home hospice care and primary care hospitalisation. Data concerning the reasons for the visits, however, remained unavailable. To estimate the proportion of visits that were related to PC, a background questionnaire was used to identify the share of primary care visits that were cancer-related. For patients, whose home municipality was different than any of those mentioned earlier (n=100; 15.9% of the patients), missing primary care costs were imputed by using average cost from the same disease state. Travelling costs related to PC visits were also included.

Private health care. Data on the use of private health care services were available from SII's registries. However, these data only cover the part of private health care usage, which the SII has reimbursed to the patients. The costs of visits related to PC were estimated as those that exceeded the control population's private health care usage and travel costs. Resource use and unit cost data were also included from the local private hospice care unit.

Medicines. Outpatient medicine costs related to PC were extracted from SII's electronic records and compared to those of the control population. The cost of medication for the treatment of PC dispensed in the hospital was extracted from hospital records.

Productivity costs

The work status of the patients and the potential retirement from work due to PC were obtained from the patient survey. Patients were asked whether they were working, retired due to cancer, retired due to other reasons or not working due to some other reason. The registries of SII were used to calculate the number of days patients were on sick leave and absent from work due to PC during the six-month observation period.

The human capital approach (HCA) was used to value loss of productivity (Hanly et al 2012). To assess the loss of productivity, gross wages (pre-tax) were translated into average labour costs by including employer's social security payments in addition to pre-tax salary (Hujanen et al 2008). Actual annual gross wages (pre-tax) were used when calculating productivity losses due to early retirement. The valuation of productivity losses due to sick leave followed the same approach, however, average daily cost of labour was based on actual wages.

Informal care

Using a background questionnaire, the patients estimated the number of weekly hours of informal care received. Informal care was defined as care that patients had received free of charge from family members and friends. These estimates were used to extrapolate the costs to the six-month observation period in each disease state.

There is no established approach for calculating the value of informal care, and the proxy good method was chosen in which the value of informal care is calculated by multiplying the number of hours of informal care by the value per hour for each care task performed. In the proxy good method the value per hour is based on the shadow price of a market substitute. This provides valuable insight into the costs of replacing informal care with formal care (Hoefman et al 2013). To value informal care, a practice nurse's mean hourly pre-tax salary was used and translated into the hourly labour cost by adding side costs on top of pre-tax salary.

4.5 Statistical methods

In general, key demographic characteristics were reported as proportions and HRQoL utility scores in different states of PC as unadjusted means, standard deviations, and 95% confidence intervals. The mean EQ-5D-3L and 15D scores and the 15D profile for each disease state were compared with those of the general population using the Student's independent samples t-test. For comparison, the samples of the general population were weighted to reflect the age, gender, and education distribution of the patient samples. The determinants of HRQoL (scores from EQ-5D-3L, 15D and VAS) were analysed using the ordinary least square (OLS) regression model. Separate models for localised and metastatic PC were built in a stepwise (backward) regression, in which the choice of predictive variables is carried out by an automatic procedure using the significant p-value of 0.10 for removal of variables. Clinical and demographic factors and EORTC symptoms served in the models as explanatory variables.

Costs were reported as the mean costs in different states of PC. The statistical significance of the differences in costs and resource use between the disease states was tested by using confidence intervals (95%). Fixed log linear multivariate models were built to analyse how background factors are associated with total costs. Total costs were used as the dependent variable and, due to skewed distribution of cost variables, natural logarithm transformation was applied. Age, cohabiting, educational level, and symptoms and functioning scales (physical, role, social, emotional and cognitive functions) measured with the EORTC QLQ-C30 were used as independent variables. Three different models were built: one for *primary* treatment, one combining *remission* and *rehabilitation*, and one for *metastatic* disease. A risk level of 5% was used for type 1 error in all analyses.

The distributions of the utility scores for each instrument are shown visually. Deviations of the utility score distributions from normal distribution were tested by using the Kolmogorov-Smirnov test and differences between the mean scores by paired samples t-tests. Skewness and kurtosis of the distributions are also reported. HRQoL instruments internal consistency was analysed with Cronbach's alpha.

The linear associations between the scores of the instruments (EQ-5D-3L and 15D) were analysed by using interclass correlation coefficient (ICC) and Pearson correlation. The ICC was performed by a two-way mixed model with absolute agreement definition and average measure. Bland and Altman plot was used to show the mean difference between paired 15D and EQ-5D-3L scores (mean difference line) and associated 95% limits of agreement (upper and lower limits), for the combined data sample.

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) (IBM Corp 2011 & 2013), and p-values ≤ 0.05 were considered statistically significant.

5. RESULTS

5.1 Patients (I-III)

A total of 1025 PC patients were approached, of whom 630 (61.5%) responded. Their ages ranged from 44 to 93 years (mean 69). Most of the participating patients had local disease and were married or cohabiting and had higher education. The mean time from diagnosis was 3.0 years and within the last 3 months, 19% of the patients had received luteinizing hormone releasing hormone (LHRH) analogue treatment, which was a commonly used option in metastatic disease. Almost half of the *Metastatic* patients had chemotherapy and a similar share in the *Palliative* group received radiotherapy. The patient characteristics by disease states are shown in table 3.

Table 3. Patient characteristics by disease states.

	<i>Primary</i>	<i>Rehabilitation</i>	<i>Remission</i>	<i>Metastatic</i>	<i>Palliative</i>	<i>All patients</i>
Respondents (%)	47	158	317	89	19	630
Demographic factors						
Age, mean (SD)	68.5 (8.2)	68.3 (8.2)	69.1 (7.8)	71.4 (7.9)	75.5 (8.3)	69.4 (8.1)
Higher education, %	28 (59.6)	52 (32.9)	173 (54.6)	48 (53.9)	7 (36.8)	279 (55.4)
Married/cohabiting, (%)	38 (80.9)	80 (50.6)	256 (80.8)	69 (77.5)	14 (73.7)	457 (82.0)
Disease-related factors						
Time after diagnosis, years (SD)	0.14 (0.5)	1.2 (0.1)	3.4 (1.0)	5.4 (4.4)	8.1 (4.5)	3.0 (2.6)
Time after metastases, years (SD)	-	-	-	2.2 (2.2)	2.6 (2.0)	2.3 (2.2)
Bone metastasis (%)	-	-	-	81 (91.0)	18 (94.7)	99 (15.7)
Treatments, within last 3 months						
Radiotherapy, (%)	0 (0.0)	3 (1.9)	2 (0.6)	10 (11.2)	8 (42.1)	23 (3.7)
Antiandrogene therapy, (%)	0 (0.0)	7 (4.4)	16 (5.0)	19 (21.3)	3 (15.5)	45 (7.1)
Zoledronic acid, (%)	0 (0.0)	0 (0.0)	0 (0.0)	17 (19.1)	2 (10.5)	19 (3.0)
LHRH-analogue, (%)	1 (2.1)	25 (15.8)	25 (7.9)	64 (71.9)	5 (26.3)	120 (19.0)
Chemotherapy, (%)	0 (0.0)	0 (0.0)	3 (0.9)	36 (40.4)	3 (15.8)	42 (6.7)

Unfortunately it was not possible to analyse the non-respondents. Access to patient records was not permitted when a patient did not want to participate and did not give an informed consent. The only analysis that was possible concerned patients' age. There was no difference between respondents and non-respondents regarding age (69.4 years vs 68.2 years, respectively).

5.2 Use of single index HRQoL instruments in PC (IV)

The literature search identified a total of 2,010 references of which 237 studies were obtained for full-text assessment. After the review of the full-text articles, 33 studies were judged to fulfil the inclusion criteria and were thus included in the qualitative synthesis of the systematic review.

Of the 33 articles, 24 (73%) utilized an indirect valuation and 16 (48%) a direct valuation method (some of the studies included both approaches). The most commonly used instrument was the EQ-5D-3L, which was used in 21 (64%) studies. The Visual Analogue Scale (VAS) was also common as it was used in ten (30%) studies. TTO was used in six (18%) studies which all originated from the USA. (Table 4).

Table 4. Summary of characteristics of publications included.

First author, year, country	Population	Number of patients	HRQoL instrument or valuation method	Follow-up period (months*)
Early/localised				
Knight et al 2004, USA	Newly diagnosed localised PC	95	TTO	0, 3, 12
Elstein et al 2005, USA	Localised PC	127	TTO	0, 3-6 months later
Korfage et al 2005, Netherlands	Localised PC	314	EQ-5D, VAS	-1, 6, 12, 52
Sommers et al 2008, USA	Localised PC	167	TTO	0
Soyupek et al 2008, Turkey	Locally advanced PC	20	15D	0
Fernández-Arjona et al 2012, Spain	Locally advanced or disseminated PC	561	EQ-5D, VAS	0
Advanced/metastatic				
Saad et al 2002, multinational	Hormone-refractory metastatic PC patients	643	EQ-5D	0, 15
Reed et al 2004, USA	Advanced PC (treatment of SRE)	1469	EQ-5D	0, every 3 months
Weinfurt et al 2005, multinational	Metastatic PC with sign of SRE	248	EQ-5D, VAS	0, 3 month up to 24 months
Sullivan et al 2007, multinational	Metastatic hormone-refractory PC patients	280	EQ-5D	0, 3, 6, 9
Namiki et al 2008, Japan	Advanced or metastatic PC	23	EQ-5D	0, 3, 6, 9 and 12
Wu et al 2008, USA	Metastatic hormone refractory PC	280	EQ-5D	0, 3, 6, 9
Färkkilä et al 2013, Finland	Palliative PC, BC, CRC	30	15D, EQ-5D, VAS	0
Skaltsa et al 2014, multinational	Metastatic castration-resistant PC	209	EQ-5D	0, 13 and every subsequent 12 week
Diels et al 2015, multinational	Metastatic castration-resistant PC	602	EQ-5D	0
Loriot et al 2015, multinational	Asymptomatic and minimally symptomatic, chemotherapy-naïve patients with metastatic castration-resistant PC	1717	EQ-5D	0, weeks 5, 13, 25, 37, 49, 61
Saad et al 2002, multinational	Hormone-refractory metastatic PC patients	643	EQ-5D	0, 15
Screening				
Booth et al 2012, Finland	PC screening	5516	15D, EQ-5D, SF-6D	surveys in 1998, 2000, 2004, 2011
Prostatectomy				
Smith et al 2002, USA	After radical prostatectomy	209	TTO, SG	0
Glazener et al 2011, UK	Radical prostatectomy or TURP	853	EQ-5D	3, 6, 9, 12
Wang & Eriksson 2014, Sweden	PC patients at least 10 years after laparoscopic radical prostatectomy	49	EQ-5D	0
Mixed/other				
Krahn et al 2003, Canada	PC	141	HUI, QWB	0
Stewart et al 2005, USA	PC, older than 60	162	SG	0
Volk et al 2004, USA	PC screening and metastatic PC	168	TTO	0
Krahn et al 2007, Canada	Three cohorts: newly diagnosed, metastatic and other	248	HUI 2/3, EQ-5D, QWB	0, 2, 12
Pearcy et al 2008, UK, Ireland	PC	25	VAS	0
Shimizu et al 2008, Japan	Localised PC and hormone refractory PC	323	EQ-5D	0
Meghani et al 2009, USA	PC or men at risk	188	TTO/VAS	single time-point
Pickard et al 2009, USA	PC	87	EQ-5D, VAS	0
Cameron et al 2012, Canada	PC patients after radiotherapy	73	EQ-5D, VAS	0, 1
Ruland et al 2013, Norway	PC and BC patients	325	15D	0, 3, 6, 12
Mickevičienė et al 2013, Lithuania	PC	501	VAS	0
Torvinen et al 2013, Finland	PC patients (different states)	630	15D, EQ-5D, VAS	0
Freytag et al 2014, USA (135)	Intermediate-risk PC	44	EQ-5D	0, 6, 12, 24, 36

EQ-5D-3L; EuroQoL; HUI; Health Utilities Index; QWB; Quality of Well-being; SF-6D; Short Form 6D, AQoL-8D; Assessment of Quality of Life
TTO; Time-Trade-off, SG; Standard Gamble, VAS; Visual Analogue Scale, PC; Prostate Cancer, BC; Breast Cancer, CRC; Colorectal Cancer

*Months if not mentioned otherwise in the text.

Based on the literature review, in localised and early stage disease, the HRQoL scores varied from 0.63 to 0.91. The impact of radical prostatectomy on HRQoL was studied in five of the articles, and the HRQoL scores after surgery varied between 0.68 and 0.91. In advanced or metastatic stage disease the HRQoL scores varied according to the literature review between 0.50 and 0.87. The variation in HRQoL scores between the various disease stages is most probably a consequence of variation in the HRQoL instruments used and variation in the study methods. These HRQoL scores can be seen only as indicative and cannot be directly compared due to different characteristics of the instruments (e.g., scales, etc.).

5.3 HRQoL in different states of PC (I)

The 15D scores of the study population ranged from 0.344 to 1.000 (mean 0.868). Altogether 30 patients (5%) were in full health (i.e., their 15D score was 1). The EQ-5D scores of the study population ranged from -0.166 to 1.00 (mean 0.845). With the EQ-5D, a ceiling effect was evident: 266 patients (42%) were in full health. The VAS score ranged from 1 to 100, with a mean of 76.4 (Table 5). 30 patients reported having full health with VAS (VAS=100). The mean scores of all instruments were consistently lower in the more advanced disease states. Instruments internal consistency was also analysed. Cronbach alpha for the 15D was 0.87, EQ-5D: 0.793, and EORTC 0.863. These results are suggesting that the instruments and their items have relatively high internal consistency. Reliability coefficient of 0.70 or higher can be considered “acceptable” in most social science research situations, but 0.80 or greater is preferred (Cortina JM 1993).

Table 5. Mean HRQoL scores in different disease states.

	EQ-5D-3L				15D				VAS			
	Mean	N	SD	95% CI	Mean	n	SD	95% CI	Mean	n	SD	95% CI
<i>Primary</i>	0.900	46	0.19	0.84-0.96	0.914	47	0.09	0.89-0.94	81.11	46	14.87	76.69-85.52
<i>Rehabilitation</i>	0.887	91	0.14	0.86-0.92	0.888	157	0.09	0.87-0.90	76.73	92	16.69	73.27-80.18
<i>Remission</i>	0.866	309	0.19	0.85-0.89	0.880	310	0.11	0.87-0.89	79.80	311	16.24	77.99-81.62
<i>Metastatic</i>	0.742	85	0.27	0.69-0.80	0.805	88	0.12	0.78-0.83	66.79	86	21.80	62.12-71.46
<i>Palliative</i>	0.590	17	0.22	0.48-0.70	0.671	19	0.10	0.62-0.72	48.67	18	19.10	39.17-58.17
<i>All patients</i>	0.845	548	0.21	0.83-0.86	0.868	621	0.11	0.89-0.94	76.36	553	18.56	74.81-77.91

However, as long as the disease was local, the mean HRQoL scores remained close to the baseline level; significantly impaired mean HRQoL scores were seen only after the disease had progressed to the metastatic stage. Both generic instruments gave higher scores in the *Primary* and *Rehabilitation* groups than those of the age- and gender-standardised general population (EQ-5D also in the *Remission* state) (Table 5). In the *Metastatic* state the mean EQ-5D and 15D scores were both clinically and statistically significantly lower than in the *Remission* state, and in the *Palliative* state, lower than in the *Metastatic* state. Lowest mean values were thus seen in the *Palliative* care state. Of the 15D dimensions, only sleeping, excretion, and sexual activity were statistically significantly worse in the *Rehabilitation* group than in the age- and gender-standardised general population. In the

Primary group, patients fared better than did the general population on the dimensions of speech, mental function, and discomfort and symptoms, and in the *Rehabilitation* group on the dimensions of mobility, vision, usual activities, mental function, discomfort and symptoms (Table 6).

Comparison against the age- and gender-standardised general population is important as it can illustrate incremental health issues in this relatively aged group. Therefore, it was somewhat surprising that in general, HRQoL was at a high level. In localised disease, PC patients' HRQoL was numerically higher or at the same level compared to general population peers with both generic instruments (EQ-5D-3L and 15D), however, when looking from a MID perspective the differences were not clinically important. When the disease progressed to metastatic state, HRQoL decreased both statistically significantly and clinically importantly.

Table 6. The mean deviations of PC patients' HRQoL scores measured by the 15D and EQ-5D-3L from those of the age- and gender-standardised general population.

	<i>Primary</i> Δ	<i>Rehabilitation</i> Δ	<i>Remission</i> Δ	<i>Metastatic</i> Δ	<i>Palliative</i> Δ
EQ-5D-3L	0.116 ***	0.060 ***	0.050 ***	-0.053 *	-0.153 **
15D index	0.025	0.012	-0.001	-0.068 ***	-0.177 ***
15D dimensions					
Mobility	0.019	0.033 ***	0.012	-0.066 **	-0.260 ***
Vision	0.008	0.036 ***	0.005	-0.003	-0.102 *
Hearing	-0.013	0.018	0.005	-0.026	-0.183 **
Breathing	0.017	0.037	0.012	-0.054 *	-0.104
Sleeping	0.012	-0.009 **	-0.026 *	-0.058 *	-0.121 *
Eating	-0.005	0.009	0.003	0.003	-0.032
Speech	0.022 ***	0.017	0.012	0.019 *	-0.056
Excretion	-0.010	-0.044 **	-0.043 ***	-0.134 ***	-0.293 ***
Usual activities	0.029	0.047 ***	0.015	-0.106 ***	-0.272 ***
Mental function	0.081 ***	0.048 ***	0.037 ***	0.021	-0.045
Discomfort and symptoms	0.082 ***	0.065 ***	0.046 ***	-0.080 ***	-0.180 ***
Depression	0.032	0.016	0.009	-0.026	-0.137 ***
Distress	0.003	0.001	-0.010	-0.029	-0.165 ***
Vitality	0.036	0.010	-0.003	-0.110 ***	-0.255 ***
Sexual activity	-0.042	-0.229 ***	-0.205 ***	-0.446 ***	-0.544 ***

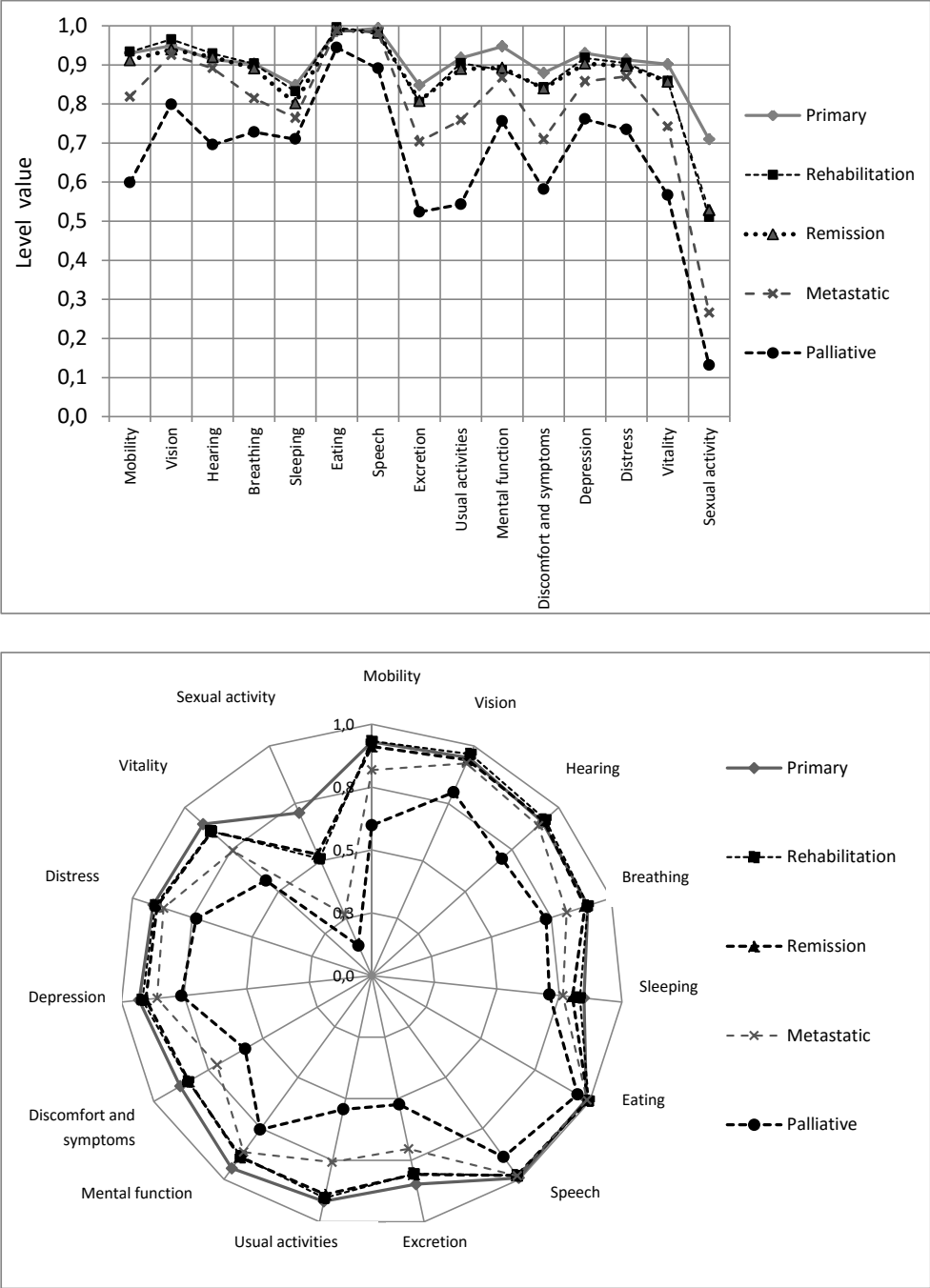
Δ, difference compared to the general population (positive for better scores compared to general population).

* = p-value < 0.05; ** = p-value < 0.01; *** = p-value < 0.005.

Graphically the 15D profiles can be produced in different ways and formats. Two different ways of illustrating the same thing are shown in Figure 5. The profiles show on what dimensions, and how severe problems (the smaller the level value, the more severe problems) the different groups of patients have. The profiles and changes in profiles are reflected in the 15D scores adjacent to the profiles.

The 15D profile highlighted the difference between local and metastatic disease in terms of decrements on different dimensions of HRQoL (Figure 5). In local disease, dimension values are close to each other with the exception of sexual activity where already *Rehabilitation* and *Remission* groups were worse off than the *Primary* group. In the *Palliative* group the values are the lowest, and patients report a lot of problems on the dimensions of mobility, excretion, usual activities, discomfort and symptoms, vitality and sexual activity.

Figure 5. The mean 15D profiles in different states of PC.



The EORTC QLQ-C30 showed that the patients with metastatic disease exhibited more symptoms than did patients with local disease; the *Palliative* group was the most symptomatic (Figure 6). Reported symptoms followed the progression of the disease stages. Only pain, diarrhoea and financial difficulties were reported more often in the *Primary* group than in the *Rehabilitation* group, and constipation occurred in the *Rehabilitation* group more often than in the *Remission* group. The mean EORTC QLQ-C30 Global Health score was 75 (range: *Primary* 81 to *Palliative* 49). The EORTC yielded different functioning scores in different disease states in line with those of the two other HRQoL instruments studied here (Figure 7).

Figure 6. EORTC QLQ-C30 functionality scales in different states of PC.

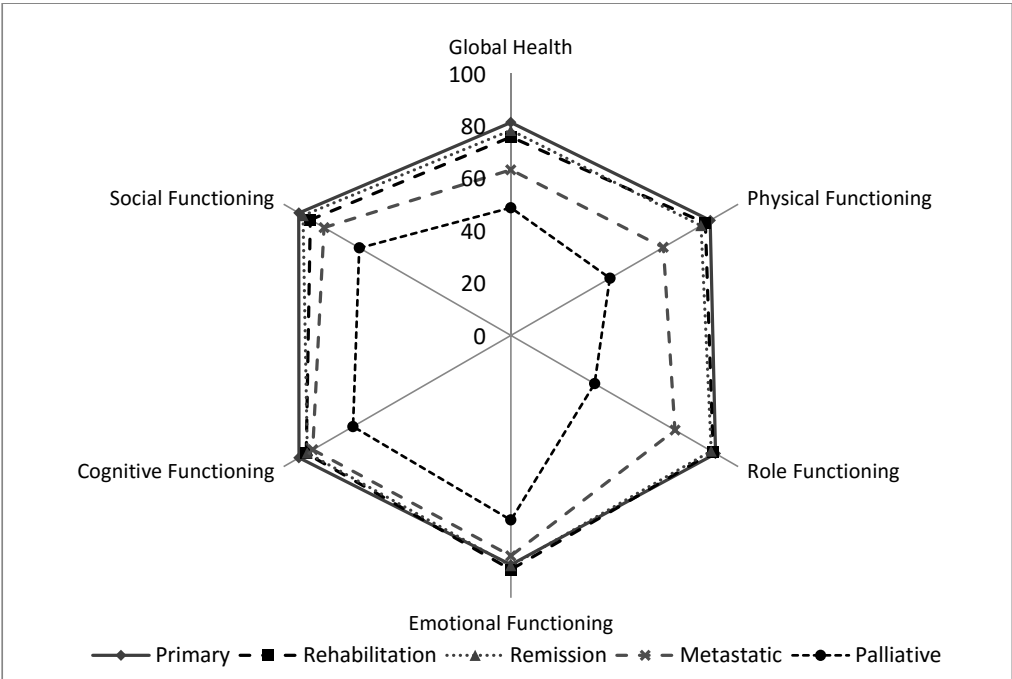
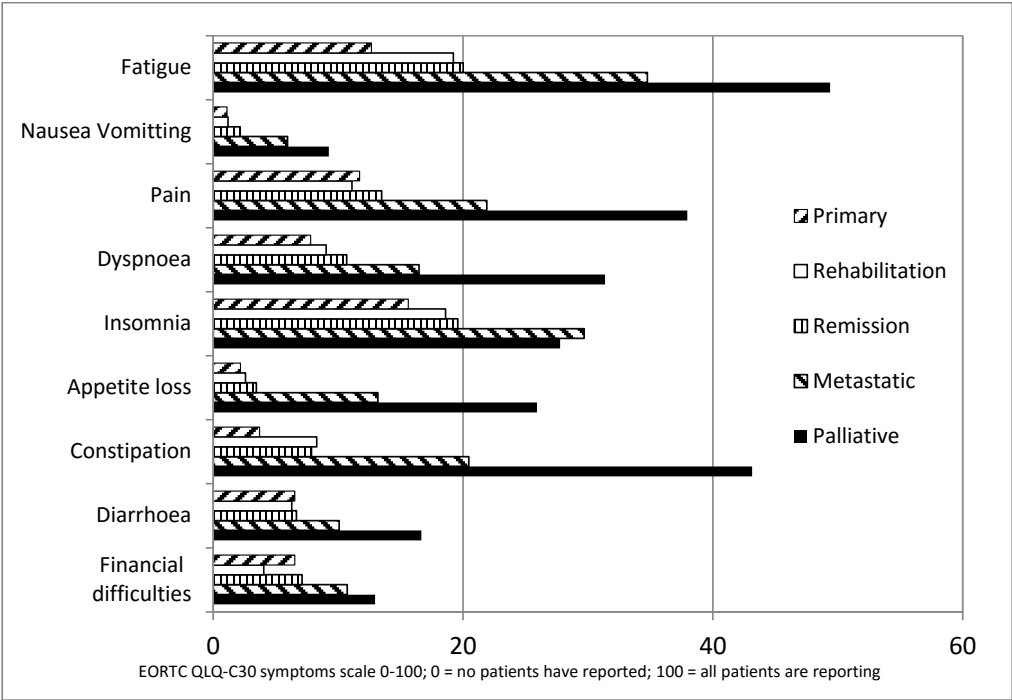


Figure 7. EORTC QLQ-C30 symptom scales in different states of PC.



5.4 HRQoL in palliative care (II)

Even with increased attention to cancer patients' HRQoL in general, so far the understanding of terminal stages of cancer is still limited. In this study the patient selection was based on two criteria: patients with metastatic disease and receiving palliative treatments only (defined by no chemotherapy or radiotherapy), and patients who died due to cancer within 6 months of responding to the questionnaire, irrespective of the treatment given. Their treatment followed routine clinical guidelines and was in no way affected by the study.

Within all three cancers (PC, CRC, BC) 311 palliative cancer patients were invited to participate, 115 (37%) responded. In addition, in the hospital palliative care unit and in the hospice, questionnaires were given to patients who were willing and capable of participating. The 15D scores were calculated for 114 patients (24% had BC, 26% had PC, and 50% had CRC), and EQ-5D and VAS scores for 111. All EORTC QLQ-C30 functioning and symptom scales were calculated for 101 patients.

Mean utility scores varied widely depending on the instrument used: the 15D gave the highest utility values and the VAS gave the lowest. The mean utility value within the study population (i.e., average within CRC, BC and PC) measured by the 15D was 0.74, and when measured by the EQ-5D-3L and the VAS, it was 0.59 and 55, respectively. The mean utility value among PC patients was 0.67 with the 15D, 0.59 with the EQ-5D-3L, and 48.7 with the VAS. All generic instruments we used were applicable for the measurement of HRQoL in end-stage cancer, however, across all patients (all 3 cancers) 13% of patients reported being in perfect health, i.e., a HRQoL score equal to 1 with the EQ-5D-3L, which raises questions on the usability of the EQ-5D-3L with end of life situations.

Of the EORTC QLQ-C30 functioning scales, physical, role, and social functionality were the most impaired among all patients. With patients closer to death, physical and role functioning deteriorated the most, while other functioning scales remained mainly unaffected. Fatigue was the most prominent symptom in each cancer group, followed by pain, and constipation (in case of PC). PC patients reported symptoms between BC (which had most symptoms) and CRC (lowest frequency of symptoms) patients. PC patients also reported less financial difficulties and diarrhoea compared with BC and CRC patients. With patients closer to death, fatigue, nausea and vomiting, pain, dyspnoea, appetite loss, and constipation were more common. Fatigue was reported by almost every patient (98%), and 82% of patients reported having at least some pain, 64% of the patients answered that they had at least some depression.

5.5 Factors associated with HRQoL (I)

The analysis based on a multivariate regression model for localised PC showed that fatigue, pain and financial difficulties were significant factors associated with HRQoL assessed with all instruments, and dyspnoea, insomnia, and age, when assessed with 15D and VAS. In a multivariate model using only the metastatic patient population (advanced disease model) fatigue and pain associated negatively with HRQoL scores assessed with all instruments. Further analysis focusing on background variables

revealed (EORTC symptoms were excluded) that not having higher education, high age and financial difficulties were the most important factors associated with decreased HRQoL scores. In advanced disease, financial difficulties and age proved to be the most significant variables.

One of the key findings was that, beyond the rather obvious factors such as symptoms and age, financial difficulties seem to be an important factor related to the poor HRQoL of PC patients.

Table 7. Factors associated with HRQoL in PC.

	EQ-5D		15D		VAS	
	Std coefficient	P-value	Std coefficient	P-value	Std coefficient	P-value
Localised disease	$R^2 = 0.564$		$R^2 = 0.738$		$R^2 = 0.471$	
Fatigue	-0.003	***	-0.002	***	-0.318	***
Dyspnoea			-0.001	***	-0.098	***
Pain	-0.003	***	-0.001	***	-0.102	***
Insomnia			-0.001	***	-0.078	***
Age	-0.002	***	-0.002	***		
Financial difficulties	-0.001	***	-0.001	***	-0.117	***
Diarrhoea			-0.001	***		
Watchful waiting			-0.023	***	-3.903	*
Cohabiting	0.037	*				
Higher education	0.028	*			2.530	*
Appetite loss	-0.002	***				
Anti-androgen treatment					-8.439	***
Time after diagnosis/recurrence					0.940	*
Constipation			-0.001	***		
Nausea vomiting			-0.001	*		
Metastatic disease	$R^2 = 0.714$		$R^2 = 0.712$		$R^2 = 0.492$	
Age			-0.002	*	-0.002	*
Fatigue	-0.005	***	-0.003	***	-0.320	***
Financial difficulties	-0.002	**				
Watchful waiting****	0.145	***				
Dyspnoea			-0.001	***		
Pain	-0.003	***	-0.001	***	-0.300	***
Anti-androgen treatment	-0.082	*				

*p-value<0.05; **=p-value<0.01; ***=p-value<0.005; ****Watchful waiting is defined as patients who do not receive any cancer treatments/operations.

5.6 Costs in different states of PC (III)

Costs reported in this study can be used in various types of analyses as they are reported as incremental costs due to cancer for a six-month period and they include direct medical costs, productivity costs and costs of informal care.

Direct health care costs

The mean total direct costs increased substantially after detection of metastases and differed markedly from the costs related to localised disease states. The costs were highest in the metastatic state of the disease (Table 8). The mean primary health care costs were relatively modest, being twice as high in newly diagnosed patients compared to the other states. Private health care costs were fairly similar to those observed in the control group. In localised disease, a small additional cost

from the use of private health care was observed. However, in the metastatic state of the disease patients used less private health care than their control group. The mean costs of medicines were lowest in recently diagnosed patients, while the mean travel costs were highest in the *Metastatic* state.

Table 8. Direct healthcare costs by disease state in PC (€).

Cost item	<i>Primary</i>	<i>Rehabilitation</i>	<i>Remission</i>	<i>Metastatic</i>
Specialist Care	2,162	539	251	2,661
(95% CI)	(1,418 – 2,906)	(345 – 734)	(165 – 336)	(2,105 – 3,217)
Primary Health Care	421	195	200	175
(95% CI)	(-80 – 921)	(55 – 355)	(104 – 295)	(115 – 234)
Private Health Care	36	42	18	-29
(95% CI)	(-21 – 93)	(-17 – 102)	(-18 – 55)	(-54 – -5)
Medication	141	307	304	4,354
(95% CI)	(-5 – 287)	(76 – 537)	(99 – 509)	(3,481–5,228)
Travelling	-10	59	-12	263
(95% CI)	(-66 – 46)	(-21 –139)	(-29 – 4)	(117 – 409)
Total Healthcare costs	2,750	1,143	760	7,423
(95% CI)	(1,853 – 3,647)	(777 – 1,508)	(479 – 1,041)	(6,199 – 8,647)

Negative value means less resource usage compared to non-PC control group (private health care and travelling costs).
All costs are for 6-month period.

Productivity costs

Most of the patients were not working which was expected considering their advanced mean age. Of the patients, 102 (16.7%) were employed and of the 430 retired patients more than two thirds were eligible for the state pension based on their age of 65 or more. Only 18 patients (2.9%) were receiving disability pension due to their cancer, and 28 patients (4.6%) were receiving disability pension due to reasons other than cancer. Seventeen patients (2.8%) reported being unemployed or not working.

The number of days absent from work due to sick leave was relatively low, being on average less than one day during the six-month period. However, in the *metastatic* group it was almost four days. The mean number of days patients were absent from work due to early retirement was much higher, being highest in the *Metastatic* and *Primary* treatment groups (8.6 and 7.7 days, respectively) (Table 9).

The estimated productivity losses were highest in the *Primary* and *Metastatic* groups (Table 9). Most of the productivity losses came from early retirement and the impact of sick leave was limited, being meaningful only in the *Metastatic* group.

Table 9. Productivity losses in PC.

	Days absent from work due to sick leave (95% CI)		Days absent from work due to early retirement (95% CI)		Total days absent from work due to PC
<i>Primary</i>	0.5	(0.47 – 1.29)	7.7	(-3.16 – 18.65)	8.20
<i>Rehabilitation</i>	0.8	(0.78 – 1.76)	4.6	(0.10 – 9.11)	5.40
<i>Remission</i>			4.0	(1.06 – 7.00)	4.00
<i>Metastatic</i>	3.9	(3.89 – 8.06)	8.6	(0.20 – 16.93)	12.50
	Productivity loss due to sick leave (95% CI), €		Productivity loss due to early retirement (95% CI), €		Total value of productivity loss, €
<i>Primary</i>	107	(101 – 276)	1,759	(-722 – 4,260)	1,866
<i>Rehabilitation</i>	171	(167 – 377)	727	(16 – 1,440)	898
<i>Remission</i>			786	(208 – 1,375)	786
<i>Metastatic</i>	834	(832 – 1,725)	3,443	(80 – 6,779)	4,278

Informal care

Only 34 patients (5.6%) received informal care due to PC either from their family or others. The mean number of hours of informal care in localised disease was modest (around one hour per week or less), but increased with disease progression, being highest in the *Metastatic* group (6.5 hours per week). The estimated value of informal care during the six-month period was highest in the patient group with advanced disease (Table 10).

Table 10. Cost of informal care in PC.

	N	Mean number of hours of informal care per week	Cost of informal care (6 months), €	(95% CI), €
<i>Primary</i>	47	1.2	589	(-506 – 1,684)
<i>Rehabilitation</i>	158	0.5	242	(-68 – 553)
<i>Remission</i>	317	1.1	540	(-217 – 1,299)
<i>Metastatic</i>	89	6.5	3,180	(110 – 6,250)

Multivariate regression analysis revealed that patient characteristics and background factors explained 9-27% of the variance in total costs associated with PC in various states of the disease (Table 11). From background factors, higher education seemed to lead to higher costs in newly diagnosed patients and cohabiting was associated with a lower cost burden in the *Metastatic* state. When analysing QLQ-C30 symptoms scales, emotional functioning in the *Primary* state was statistically significantly positively associated with costs, whereas physical functioning in the *Remission/Rehabilitation* state was significantly negatively associated with costs. Regarding QLQ-C30 functionality scales, costs were statistically significantly higher when patients reported more nausea/vomiting and financial difficulties in the *Remission/Rehabilitation* state.

Table 11. The results of multivariate analyses of cost drivers with the natural logarithm of total costs as the dependent variable (PC).

Variable	Primary treatments		Remission/ Rehabilitation		Metastatic	
	Coefficient	P-value	Coefficient	P-value	Coefficient	P-value
	R² = 0.273		R² = 0.151		R² = 0.089	
(Constant)	9.050		8.555		9.737	
Characteristics						
Age, years	-0.130	0.551	-0.089	0.071	-0.071	0.586
Cohabiting	0.155	0.305	-0.047	0.307	-0.308	0.015 *
Higher education	0.443	0.012 *	-0.019	0.686	0.058	0.645
QLQ-C30 Symptom scales						
Global health	0.326	0.225	-0.030	0.645	-0.129	0.473
Physical functioning	0.021	0.951	-0.210	0.003 *	-0.105	0.640
Role functioning	-0.431	0.136	-0.014	0.851	0.073	0.770
Emotional functioning	0.469	0.012 *	0.117	0.074	0.123	0.566
Cognitive functioning	-0.406	0.115	-0.013	0.831	0.147	0.424
Social functioning	-0.183	0.256	-0.019	0.747	-0.253	0.158
QLQ-C30 Functionality scales						
Fatigue	-0.041	0.882	-0.016	0.801	-0.103	0.562
Nausea/vomiting	-0.113	0.547	0.274	0.000 *	-0.045	0.750
Pain	0.448	0.062	-0.055	0.302	0.139	0.381
Dyspnoea	0.095	0.685	-0.032	0.534	0.214	0.164
Insomnia	-0.239	0.372	0.026	0.622	-0.089	0.484
Appetite loss	-0.043	0.848	0.067	0.199	0.173	0.270
Constipation	-0.072	0.650	-0.027	0.558	0.195	0.145
Diarrhoea	-0.056	0.698	0.040	0.373	0.168	0.199
Financial difficulties	0.227	0.209	0.107	0.034 *	-0.041	0.748

*=p-value<0.05

The share of productivity costs out of total costs (combined direct health care costs and productivity costs) varied between 37% and 51% in different states of the disease. However, when informal care costs were also included, the share of indirect costs (productivity costs and informal care costs) increased to 47–64% out of total costs (combination of direct health care costs, productivity costs and informal costs).

Based on the results, direct costs for a six-month period in localised PC, especially in the early treatment phase, may not be as high as in the case of some other cancers (e.g., CRC etc.)(Färkkilä et al 2015). Also, the estimates for a six-month period in the subsequent states (*Rehabilitation* and *Remission*) show that resource use is moderate and the costs of interventions or adjuvant medications used in PC are relatively modest. The costs, however, started to accumulate when the disease progresses.

Productivity loss due to sick leave was modest, however, more losses being generated by early retirement. Overall, only 177 patients (29%) were younger than 65 years, and consequently still below the general retirement age, and only 17% of the total number of patients were working, curtailing the potential productivity losses.

Direct costs related to different states of PC are significant and productivity losses and costs of informal care play a major role when estimating the total burden of PC. Excluding such a large share

of costs from cost effectiveness considerations might have a significant impact on the decision making process of health economic evaluations or health technology assessments (HTA).

5.7 Characteristics and interchangeability of the EQ-5D and 15D (I)

One aim of this thesis was to describe differences between two generic HRQoL instruments (EQ-5D-3L and 15D) in PC, and to evaluate whether they can be used interchangeably. The mean utility scores were close to each other (EQ-5D-3L: 0.845; 15D: 0.868), and they correlated fairly well (Pearson correlation $r = 0.714$). The distribution of the scores differed from normal although the distribution of the 15D scores was closer to normal than that of the EQ-5D-3L scores. There was a moderate agreement between the scores (Interclass correlation coefficient (ICC) = 0.752). Internal consistencies were analysed for HRQoL instruments and Cronbach alphas were for the 15D: 0.870, EQ-5D: 0.793, and EORTC QLQ-C30: 0.863. These results are suggesting that the instruments and their items have relatively high internal consistency. Nevertheless, the study results suggest that the two studied instruments cannot to be used interchangeably, or at least such an approach needs to be taken cautiously.

Discrimination

In localised disease (higher HRQoL) there were only small differences in the mean scores between the instruments, but after the disease progresses to a metastatic stage (lower HRQoL) more differences can be found (e.g., Table 5). For example, among patients who received palliative care, the EQ-5D-3L produced a much lower mean score (0.590) compared to the 15D (0.671). This was seen already in the metastatic state, where the mean 15D score started to decrease from that observed in localised disease. These results suggest that differences between instruments in the mean scores, especially in the lower end of the utility range, are both statistically significant (paired t-test) and clinically important.

The proportion of high HRQoL scores (EQ-5D/15D ≥ 0.75) was higher with the 15D than with the EQ-5D. However, HRQoL scores above 0.5 were almost as prevalent with the 15D (99%) as with the EQ-5D-3L (96%).

Table 12. Comparison of utility values in PC (mean).

HRQoL instrument	EQ-5D-3L	15D
% share of the utility values in the following subgroups		
≥ 0.75	72.4%	85.0%
0.5-0.74	23.5%	14.0%
0.25-0.49	1.1%	1.0%
0-0.24	1.8%	-
<0	1.1%	-

Plotted distributions of the 15D and the EQ-5D-3L scores in PC are shown in Figures 8 and 9. The Kolmogorov-Smirnov test was used to confirm that both distributions differed from a normal distribution, but the 15D distribution clearly less. Both distributions were negatively skewed (15D - 1.118, EQ-5D-3L -2.134) indicating long left-hand tails which are also visually apparent. Kurtosis (15D 1.141, EQ-5D-3L 6.361) suggested that the relatively large standard deviation of the EQ-5D-3L can result from infrequent extreme deviations.

Figure 8. Distribution of the HRQoL scores with 15D in PC.

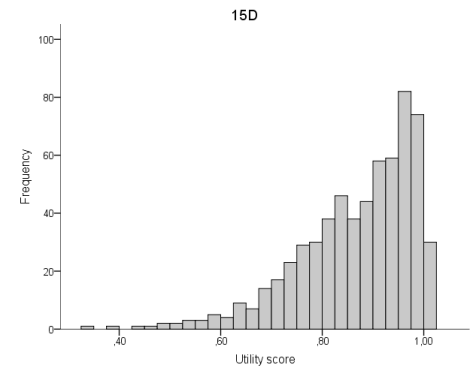
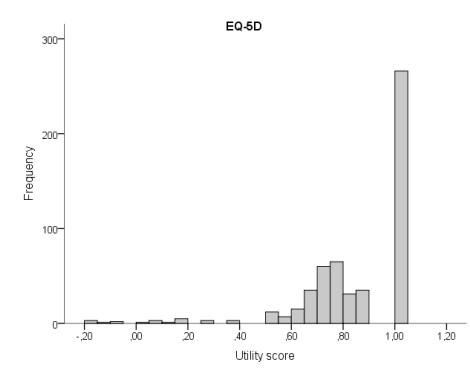


Figure 9. Distribution of the HRQoL scores with EQ-5D-3L in PC.



Agreement of HRQoL scores between the EQ-5D and the 15D

The distribution of the HRQoL scores produced using the EQ-5D-3L was discontinuous, had a long tail with low HRQoL scores and a peak with the highest possible HRQoL score. The long tail is partly explained by health states with negative EQ-5D-3L scores. The share of negative HRQoL scores was 1.1% using the EQ-5D-3L. The distribution for the 15D was continuous, slightly skewed to the right and very low HRQoL scores were missing (only 1% between 0.25 and 0.49). The Bland–Altman graphical method verified the differences between the instruments. The dissimilarities between the scores for the instruments were particularly evident at both ends of the measurement scales (Figure 10).

Figure 10. Bland-Altman plot.

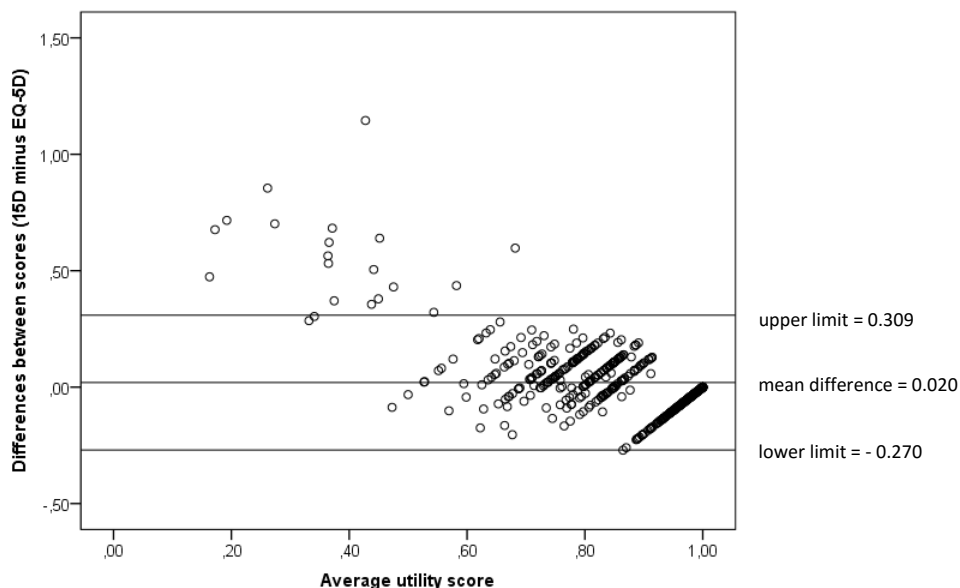


Figure 10. Bland and Altman plot showing the mean difference between paired 15D and EQ-5D scores (mean difference line) and associated 95% limits of agreement (upper and lower limits), for the combined data sample. The markers represent the difference between scores and the average of the scores for each paired observation.

Association

The association between the EQ-5D-3L and the 15D scores was relatively good (ICC = 0.75). The linear correlation (Pearson) between the two was 0.714. In the lower end of the utility range the linear correlation decreased. All these correlations were statistically significant ($p < 0.01$).

The ceiling effect (the percentage of patients in full health, i.e., score = 1) was prominent with the EQ-5D-3L: 266 patients (42%) obtained the score of full health (=1), whereas with the 15D this was 5%. A floor effect was not seen, although 6 (1%) patients obtained an EQ-5D-3L score < 0 (0 = being dead, < 0 = worse than being dead).

6. DISCUSSION

This study revealed that the use of generic HRQoL instruments in PC research has been limited. HTA bodies and European authorities are increasingly demanding evidence on cost-effectiveness, and CUA has gained ground as the method of choice when assessments are performed. For CUA, QALYs are needed, and sometimes HTA bodies may require that they are based on assessments performed by certain pre-defined instrument (e.g., EQ-5D-3L for NICE). Based on the literature review, such data may be limited, and the use of mapping algorithms may be more frequent in the future.

PC patients' HRQoL remained at a relatively high level as long as the patients' disease remained localised. The 15D produced higher scores compared to the EQ-5D-3L in general. In localised disease HRQoL was at a similar level as that of the age- and gender-standardised general population. One explanation for this finding could be that a significant proportion of patients enter PC treatment because of elevated prostate-specific antigen (PSA) levels found in opportunistic testing, and have minor or no symptoms at all that would impair HRQoL. As PSA testing has not been recommended at the national level, such an opportunistic testing in Finland is currently limited mainly to occupational health services. Based on the Finnish national health survey, localised PC patients also valued their HRQoL higher than did patients with other types of cancer (Saarni et al 2006). This study provides detailed information on PC patients' HRQoL with different instruments in different states of disease, and this data can be used also outside Finland in health economic analyses.

In Finland the cost burden of PC has been mainly evaluated in the context of other cancers and this study complement that research. Stage specific HRQoL data or incremental costs compared to age-standardised peers have not been presented before in Finland. Some earlier estimates on cost burden have been presented and based on that it seems that PC generates a major share of the cancer cost burden for the society (Mäklin & Rissanen 2006; Syöpätautien asiantuntijaryhmä 2014). This is expected as PC is one of the most prevalent cancers. The total healthcare costs per patient were relatively modest in the *Rehabilitation* and *Remission* groups, but naturally higher in groups where more active treatment interventions take place (i.e., after diagnosis and when the disease becomes metastatic). The cost results of this study are presented as incremental costs due to PC compared to age, gender and place of residence standardised general population peers and are in agreement with some previous estimates (Luengo-Fernandez et al 2013; Mehra et al 2013).

The literature review on single index HRQoL instruments

The literature search identified over 2000 studies on HRQoL of PC patients, but only 33 of them were eligible for the final systematic review. The most commonly used instrument in those studies was the EQ-5D-3L, which was used in 21 studies. Based on the literature, in localised PC disease-specific domains like urinary, sexual and bowel function are the most profoundly affected domains, whereas, with some exceptions, general HRQoL usually remains mostly unaffected (Eton & Lepore 2002; Torvinen et al 2013). The substantial disutility of asymptomatic disease observed in one study was thought to reflect more the anxiety caused by the uncertainty of not knowing whether the cancer would spread than the current actual state of health (Steward et al 2005). Krahn et al (2003) concluded that although sexual, urinary and bowel dysfunction are common in PC, their impact on

overall health status may have been overestimated if utility scores have been derived from hypothetical scenarios or from individuals without the disease. For localised and early stage disease, the HRQoL scores reported in the literature were relatively well in agreement with the 15D and EQ-5D-3L results observed for localised disease in this study. The sexual activity dimension was naturally affected in the 15D as low values were reported already when the disease was local, but especially after detection of metastases. Longitudinal follow-up studies on HRQoL are needed to draw more accurate conclusions on the HRQoL impact of the side effects of the treatments in localised and early PC (Korfage et al 2005).

In the advanced or metastatic PC, many of the reviewed articles focused on the HRQoL effects of skeletal-related events (SREs) and found a significant impact of SREs on HRQoL (Reed et al 2005; Weinfurt et al 2005; Sullivan et al 2007), although in the study by Saad et al (2002), the observed deterioration of HRQoL in patients with SREs was not statistically significant. One might argue that this may be due to the insensitivity of the generic EQ-5D-3L instrument that was used, but Weinfurt et al (2005), and Sullivan et al (2007), found a significant HRQoL impact related to SREs using the same instrument. Pain is a frequent symptom associated with SREs, and many HRQoL studies therefore incorporate also disease-specific instruments, such as the Brief Pain Inventory (BPI) or the EORTC QLQ-C30, which include a pain domain. In this study over 20% of the patients reported pain in the *Metastatic*, and roughly half in the *Palliative* group (EORTC QLQ-C30).

Costs

The total costs varied quite substantially between the disease states. Results support previous findings that PC is an expensive cancer to treat, especially in the advanced state (Kalso et al 2011). Total direct health care costs for a six-month period varied between €760 and €7,423 depending on the state of the disease. Direct costs in localised PC, especially in the early treatment phase, however, may not be as high as in the case in some other cancers (i.e., CRC, etc.) (Färkkilä et al 2015).

Productivity losses varied between disease states, and were fairly low in localised disease but naturally increased in advanced disease states. The share of productivity losses out of all costs was prominent (47-64%). There is uncertainty over how to assess productivity losses, and according to Hanly et al (2012), results may differ substantially between approaches. However, so far there is no consensus on this topic and the human capital approach was chosen as being the most commonly used. It has been estimated that indirect costs may result in up to 70% of the total burden of disease in breast cancer patients (Lidgren et al 2007). These results can be considered to be on the same level compared to the indirect (productivity) costs observed in this study.

The costs of informal care have been less studied than direct costs or productivity losses, but they may add significantly to the total cost burden of the disease. On average, the total number of hours of informal care received was very modest, which, however, was not true for those 34 (6%) patients, who actually received such care and used it intensively. Most of these patients had more advanced disease. As clinical information was not collected, it is not possible to evaluate why these patients needed this amount of informal care or whether other patients received some other type of support that this study was not able to capture. Nevertheless, informal care plays an important part in the support network of PC patients and more research is needed to reveal its true role. A recent study

also indicates that improving the health of the patient reduces informal care needed (Rowen et al 2016a).

HRQoL results

The EORTC QLQ-C30 showed that the patients with metastatic disease exhibited more symptoms than did patients with local disease. Reported symptoms followed the progression of the disease stages. Only pain, diarrhoea and financial difficulties were reported more often in the *Primary* group than in the *Rehabilitation* group, and constipation occurred in the *Rehabilitation* group more often than in the *Remission* group. Fatigue was reported by around one fifth of the patients with local disease, but by approximately 40% after metastasis. Nausea and vomiting were relatively infrequent in all patient groups and less than 10% reported it in metastatic disease state, in which around half of the patients were receiving chemotherapy. It seems that anti-nausea medications are used effectively and patients are able to undergo treatments as planned. Around 20% of the patients were reporting insomnia.

The generic instruments, EQ-5D-3L and 15D, produced results which are in-line with the results of previous studies included in the literature review. In local disease, HRQoL is at a relatively high level and comparable to that of age-matched peers. In advanced disease, the mean HRQoL scores were clinically importantly and statistically significantly lower than in patients with localised disease. The variation in HRQoL scores between the various disease states is most probably partly also explained by the different HRQoL instruments used. The HRQoL deterioration was most pronounced in patients in whom the disease had progressed to the palliative care state. In palliative care, PC patients' HRQoL was lower compared to that observed in CRC patients, but at the same level as in BC patients. One reason for this could be bone metastases, which are more common in BC and PC compared to CRC. This finding was supported by lower functionality scales and more symptoms in PC and BC patients. In general, there was no data available from these instruments in the palliative patient group. End-of-life patients were able to answer the study questionnaire (altogether 76 questions) and the answers were consistent with all instruments, which can be interpreted that all instruments are applicable to this patient group. However, a high ceiling effect for the EQ-5D-3L is something that questions the validity of the EQ-5D-3L in the HRQoL measurement of end-of-life patients'.

This study aimed at generating HRQoL data in different states of the disease and therefore analysis of the impact of different treatment options (surgery, radiation etc.) on the HRQoL was out of scope of the study. Further research is needed to provide more information on this topic as it could inform patients and physicians on the potential consequences of the different treatment choices. These study results serve better health economic analysis than individual treatment choices but reveal some general information regarding HRQoL in different states of the disease (e.g., symptoms that affect HRQoL in different states).

Interchangeability of the EQ-5D-3L and 15D

European authorities, individual countries and local agencies are currently not in the same phase regarding the use of health economic/health technology assessments. There are efforts towards European-wide assessments (e.g., EMA, EUnetHTA), local agencies are implementing cost-effectiveness assessments, and for instance NICE in the United Kingdom, is moving to value-based assessment. This is interesting, as NICE has recommended that burden of illness (BOI) should be used to weight QALY gain in future value-based assessment (Rowen et al 2016b). At the same time, for instance Spain has followed a different path and walked away from using QALYs in HTAs, like Germany and the US did already earlier.

This study corroborated earlier findings that there are considerable differences in the results produced by the HRQoL instruments - one of the most evident was the ceiling effect: 42% of the patients were in full health according to the EQ-5D-3L, but only 5% according to the 15D. Even within palliative patients, the ceiling effect with the EQ-5D-3L was prominent, 13%. In the light of such findings, the validity of EQ-5D-3L is questionable for these patient groups. In general, these findings are in-line with previous studies and result from the different features of the instruments, mainly different descriptive systems (questionnaires) and ranges of health state values and the shape of the distribution of scores (Conner-Spady & Suarez-Almazor 2003; Brazier et al 2004; Marra et al 2004; Tsuchiya et al 2006; Lillegraven et al 2010; Vainiola et al 2010). In comparison between EQ-5D-3L and 15D, the mean utility scores were close to each other, and correlated fairly well. The distribution of the scores differed from normal although the distribution of the 15D scores was closer to normal distribution than that of the EQ-5D-3L scores. There was moderate agreement between the scores. As measured by the number of health states defined by the instrument, the health state descriptive system of the 15D is much richer, especially in comparison with the EQ-5D-3L. The valuation space of the EQ-5D-3L (-0.59–1.00) is about 60% longer than that (0–1) of the 15D.

Based on the results, the EQ-5D-3L and the 15D should not be considered interchangeable in health economic evaluations, especially in cases where HRQoL values are low, or differ significantly from those of age-standardised peers. The marked ceiling effect, discontinuous distribution of EQ-5D-3L scores divided into two main groups, as well as the higher HRQoL scores obtained by the 15D compared to EQ-5D-3L, and no scores between 0.88 and 1.00 for the EQ-5D-3L (a joint effect of the health state descriptive system and valuation system), are findings that have been earlier reported also in other diseases (Saarni et al 2006; Vainiola et al 2010; Heiskanen et al 2016). These differences need to be taken into consideration when these instruments and their results are used in health economic evaluations. However, further research should be performed as this study is lacking information on HRQoL instruments responsiveness over time. Nevertheless, in daily clinical practice, the proportion of patients reaching the positive MID (EQ-5D-3L: 0.08, 15D: 0.015) could be a more patient-centric outcome for monitoring clinical success than the cumulative numbers of QALYs gained (Heiskanen et al 2016).

Factors associated with HRQoL

For the analysis of factors affecting HRQoL across different disease states and different instruments, two linear ordinary least squares (OLS) regression models were developed: one for local disease and the other for metastatic disease. The analyses revealed that beyond symptoms, financial difficulties

and age were the most important explanatory factors impairing HRQoL in both regression models. These results are in line with those of earlier published studies (Jayadevappa et al 2005; Song et al 2011). Treatment options failed to explain the variance in patients' HRQoL values. The OLS regression approach may have its limitations as the distributions of the scores produced by the generic instruments analysed here, especially the EQ-5D-3L, failed to satisfy the distributional assumptions required by traditional OLS. Although, based on the literature, the choice of using a more complex regression method has rather little significance for the 15D, this may not hold true for the EQ-5D-3L (Saarni et al 2006).

One of the key findings was that beyond the rather obvious factors such as symptoms and age, financial difficulties seem to be an important determinant related to the poor HRQoL of PC patients. In palliative care symptoms, especially fatigue, will lead to impairment of both activities of daily living and psychological functioning, and therefore fatigue seems to be the most significant factor deteriorating HRQoL, whereas clinical and demographic factors had less effect on HRQoL. Furthermore, patients' functionality, as measured by the EORTC QLQ-C30, was also impaired, especially in the physical, role, and social dimensions. This was also evident when the study results were compared with the general population reference values available from Germany and Sweden (Michelson et al 2000; Schwarz & Hinz 2002).

Strengths and limitations of the study

The most important limitation of the study is the cross-sectional study design. It might have been more effective to follow the same patients throughout their disease progression. However, this would have needed a much longer follow-up time. As this was a cross-sectional study, it was not possible to analyse HRQoL instruments responsiveness to change. The response rate was 61.5%, which can also be seen as a limitation. Analysis of the ages revealed that there were no differences between responders and non-responders but unfortunately it was not possible to do further analysis without consent to participate to study. Although there are no reasons to believe that absence of non-responders would have impacted the study results.

One potential limitation could also be the use of the UK TTO tariff for EQ-5D-3L, especially in terms of comparing results with the 15D in a Finnish setting. However, there is no local TTO tariff available and also most previous EQ-5D-3L studies in Finland have used the UK TTO tariff. Currently there is also a five level (five answer options per question) version (EQ-5D-5L) available (Herdman et al 2011), however, the country-specific value sets are lacking and therefore the use of this newer version is limited at the moment. For instance NICE has expressed in 2017 that they will continue for the time being to recommend the 3-level as the basis for submissions (EuroQol 2017).

A key strength on this study is the holistic approach; having two generic HRQoL instruments (15D and EQ-5D-3L) and a disease-specific instrument (EORTC QLQ-C30). They allow different types of analyses, and also a comparison of results obtained with different instruments. Our analysis of cost data can be judged to be robust and includes direct costs, productivity costs and cost of informal care. What makes this unique is the use of a control group that allow to focus on costs that are driven by PC in this fairly aged population which uses health care services regardless of PC on a regular basis.

The fact that the patients were not categorised inside the five disease states according to treatments they had received and the analyses included all the patients representing the real-life situation in PC care, can also be seen as a strength of the study. Most other analyses are limited to study certain interventions and patients are included or excluded according to the intervention that is under evaluation. Although this gives a robust estimate of the efficacy of the intervention, it does not reflect the everyday situation in health care units, where different types of PC patients are treated with multiple interventions.

Transferability of the results outside Finland depends on the need of the data. Cost data are typically reflecting efficiency of the health care system and should be used with caution outside the system where they have been collected. HRQoL data are something that is currently often used across borders. There the key for using these data is to standardise treatments and/or disease states to be able to reliably estimate that the target patient population is similar to the source population.

In general, the internal consistency of the HRQoL questionnaires was at a good level as measured by Cronbach's alpha. All these questionnaires have been validated earlier and these results can be used to depict the HRQoL of these patient groups with robust external validity. Differences and the agreement between instruments were analysed in different ways (e.g., ICC and Bland-Altman plot). In general, there were no major reasons to question the internal validity, i.e., credibility, of the findings obtained with these instruments. An exception is the high ceiling effects with the EQ-5D-3L in seriously ill patient groups, where one would not expect a high number of scores indicating full health.

Cost data from hospital registries and other registries can be divided into two parts: volumes (e.g., number of treatments) and unit cost. First ones are reliable and bias could come from miscoding, while latter ones can be challenged to be as good as methods that were used to estimate or calculate those unit costs (e.g., how well are the hospitals able to calculate resources used for producing different services or procedures). In general there are no reasons to believe that there would be any systematic bias or that prices would not be based on the best estimate on the production cost behind them. For example public hospitals are owned by the municipalities and prices should reflect the production cost of these services. Similarly prices of the drugs are true prices that are paid by the society. When estimating the amount of productivity losses incurred or informal care obtained, it is not so easy to verify what is the most appropriate method to estimate them. Nevertheless, labor cost was based on real wages (pre-tax gross) and employer's social security payments and this method is as realistic as possible, but of course there are some limitations when using the human capital approach. Calculations of productivity losses caused by early retirement and sick leaves followed more or less the same approach. Similarly, the number of hours of informal care obtained was based on a questionnaire which could be challenged as patients were asked to report the amount of services used during the last three months. In terms of cost data, the external validity i.e., transferability and generalizability can be challenged unless the environment can be controlled or matched with the source situation.

The study results give important baseline information regarding costs and HRQoL in different states of disease. The results can be compared, combined or used as an alternative/supportive data set in any health economic / cost analysis dealing within PC. If combined with national epidemiological

data, these data could be used even e.g., when analyzing potential cost-effectiveness of screening of PC or to support how to optimize PC management at the national level.

7. CONCLUSIONS AND IMPLICATIONS

- HRQoL assessments in PC, especially in the context of preference-based single index measures that can be used directly for QALY estimations, are scarce. Given the fact that PC is one of the most common cancers, it is important to focus on the treatment options and on their unique effects on the quantity and quality of life, while not forgetting the evaluation of the cost-effectiveness of these options.
- All evaluated HRQoL instruments in this study provided valuable insight into patients' overall HRQoL. Symptoms of fatigue and pain, and background variables of financial difficulties and age were the most important factors associated with poor HRQoL.
- Direct costs related to different states of PC are significant. However, productivity losses and costs of informal care also play a major role when estimating the total burden of PC. Excluding such a large share of costs from cost effectiveness considerations might have a significant impact on the decision making process of health economic evaluations or HTA.
- Additional studies are still needed to better appreciate the impact of the increasing economic burden of PC management. The aging of the population will substantially increase the demand for all health care resources, and PC is definitely one of the areas where a significant number of patients will be diagnosed and treated. Also the rational use of screening should be kept in evaluations. From a health policy perspective, more research is needed to make appropriate choices on allocation decisions to guarantee the rational use of health care resources.
- In the end-of-life care, some differences between cancer types were found: CRC patients reported slightly higher mean utility scores than BC and PC patients. Several reasons could account for this: symptom burden was lowest in CRC patients, bone metastases known to be painful were less frequent, and the time from primary diagnosis and first metastasis was shorter than in BC and PC patients. In comparison, BC patients were the most symptomatic and had the most impaired HRQoL, which might, at least partly, be explained by the longer duration of the sickness in BC, younger age, and the predisposition to bone metastases.
- Generic HRQoL instruments (EQ-5D-3L and the 15D) should not be considered interchangeable in health economic evaluations, especially in the case where HRQoL values are low or differ significantly from those of age-standardised peers. For instance in end-of-life care, the EQ-5D resulted in a 13% ceiling effect. The EQ-5D-3L produces greater differences in utilities than the 15D. The marked ceiling effect and the two-peaked, discontinuous distribution of the EQ-5D-3L scores, as well as the higher HRQoL scores obtained by the 15D compared to EQ-5D-3L, have been earlier reported in other diseases. Thus, these differences need to be taken into consideration when these instruments and their results are used in health economic evaluations.

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TUTKIMUS ELÄMÄNLAADUSTA JA KUSTANNUKSISTA

SUOSTUMUS JA KYSELYLOMAKKEET



HELSINGIN JA UUDENMAAN SAIRAANHOITOPIIRI



SUOSTUMUS

Tutkimukseen osallistumien ja henkilötietojen käsittely

Minua on pyydetty osallistumaan tutkimukseen, jossa selvitetään kyselyn avulla potilaiden elämänlaatua, kustannuksia ja oirekuva. Olen saanut tätä tutkimusta ja sen yhteydessä suoritettavaa tietojen keruuta ja käsittelyä kuvaavan tutkimustiedotteen.

Suostun vapaaehtoisesti osallistumaan tutkimukseen ja annan suostumukseni tutkimuksen yhteydessä tapahtuvaan tietojen keräämiseen ja niiden käsittelyyn. Voin myöhemmin peruuttaa suostumukseni sen vaikuttamatta mitenkään saamaani hoitoon.

Annan tällä suostumuksella luvan siihen, että oheisilla kyselylomakkeilla kerätyt tiedot saadaan yhdistää muihin minua koskeviin Helsingin ja Uudenmaan sairaanhoitopiirissä oleviin hoitotietoihin sekä Tilastokeskuksen, Terveystieteiden ja hyvinvoinnin laitoksen (THL) ja Kansaneläkelaitoksen (KELA) sekä kotikuntani sairauteni hoitoa koskeviin tietoihin. Ymmärrän, että henkilötunnuksella varustettu tieto tulee vain tutkimusryhmän tietoon ja, että tiedot tallennetaan erityistä salattua potilastunnusta käyttäen, jolloin niistä ei voi päätellä henkilöllisyyttäni.

Suostumuksen antaja täyttää

Paikka ja aika	Allekirjoitus
Henkilötunnus (xxxxxx-xxx)	Sukunimi, Etunimi
Osoite	

Olkaa ystävällinen ja palauttakaa tämä suostumuslomake yhdessä täytetyn kyselylomakkeen kanssa.

Täytetään HUS:ssa

Paikka ja aika	Suostumuksen vastaanottajan allekirjoitus
Nimenselvitys	



TERVEYTEEN LIITTYVÄN ELÄMÄNLAADUN KYSELYLOMAKE (15D©)

Lukekaa ensin läpi huolellisesti kunkin kysymyksen kaikki vastausvaihtoehdot. Merkitkää sitten rasti (x) sen vaihtoehdon kohdalle, joka parhaiten kuvaa nykyistä terveydentilaanne. On tärkeää, että vastaatte kaikkiin 15 kysymykseen rastittamalla kustakin yhden vaihtoehdon.

1. Liikuntakyky

- 1 ☐ Pystyn kävelemään normaalisti (vaikeuksitta) sisällä, ulkona ja portaissa.
- 2 ☐ Pystyn kävelemään vaikeuksitta sisällä, mutta ulkona ja/tai portaissa on pieniä vaikeuksia.
- 3 ☐ Pystyn kävelemään ilman apua sisällä (apuvälinein tai ilman), mutta ulkona ja/tai portaissa melkoisin vaikeuksin tai toisen avustamana.
- 4 ☐ Pystyn kävelemään sisälläkin vain toisen avustamana.
- 5 ☐ Olen täysin liikuntakyvytön ja vuoteenoma.

2. Näkö

- 1 ☐ Näen normaalisti eli näen lukea lehteä ja TV:n tekstejä vaikeuksitta (silmälaseilla tai ilman).
- 2 ☐ Näen lukea lehteä ja/tai TV:n tekstejä pienin vaikeuksin (silmälaseilla tai ilman).
- 3 ☐ Näen lukea lehteä ja/tai TV:n tekstejä huomattavin vaikeuksin (silmälaseilla tai ilman).
- 4 ☐ En näe lukea lehteä enkä TV:n tekstejä ilman silmälaseja tai niiden kanssa, mutta näen kulkea ilman opasta.
- 5 ☐ En näe kulkea oppaatta eli olen lähes tai täysin sokea.

3. Kuulo

- 1 ☐ Kuulen normaalisti eli kuulen hyvin normaalia puheääntä (kuulokojeella tai ilman).
- 2 ☐ Kuulen normaalia puheääntä pienin vaikeuksin.
- 3 ☐ Minun on melko vaikea kuulla normaalia puheääntä, keskustelussa on käytettävä normaalia kovempaa puheääntä.
- 4 ☐ Kuulen kovaakin puheääntä heikosti; olen melkein kuuro.
- 5 ☐ Olen täysin kuuro.

4. Hengitys

- 1 ☐ Pystyn hengittämään normaalisti eli minulla ei ole hengenahdistusta eikä muita hengitysvaikeuksia.
- 2 ☐ Minulla on hengenahdistusta raskaassa työssä tai urheillessa, reippaassa kävelyssä tasamaalla tai lievässä ylämäessä.
- 3 ☐ Minulla on hengenahdistusta, kun kävelen tasamaalla samaa vauhtia kuin muut ikäiseni.
- 4 ☐ Minulla on hengenahdistusta pienenkin rasituksen jälkeen, esim. peseytyessä tai pukeutuessa.
- 5 ☐ Minulla on hengenahdistusta lähes koko ajan, myös levossa.



5. Nukkuminen

- 1 ☐ Nukun normaalisti eli minulla ei ole mitään ongelmia unen suhteen.
- 2 ☐ Minulla on lieviä uniongelmia, esim. nukahtamisvaikeuksia tai satunnaista yöheräilyä.
- 3 ☐ Minulla on melkoisia uniongelmia, esim. nukun levottomasti tai uni ei tunnu riittävältä.
- 4 ☐ Minulla on suuria uniongelmia, esim. joudun käyttämään usein tai säännöllisesti unilääkettä, herään säännöllisesti yöllä ja/tai aamuisin liian varhain.
- 5 ☐ Kärsin vaikeasta unettomuudesta, esim. unilääkkeiden runsaasta käytöstä huolimatta nukkuminen on lähes mahdotonta, valvon suurimman osan yöstä.

6. Syöminen

- 1 ☐ Pystyn syömään normaalisti eli itse ilman mitään vaikeuksia.
- 2 ☐ Pystyn syömään itse pienin vaikeuksin (esim. hitaasti, kömpelösti, vavisten tai erityisapuneuvoin).
- 3 ☐ Tarvitsen hieman toisen apua syömisessä.
- 4 ☐ En pysty syömään itse lainkaan, vaan minua pitää syöttää.
- 5 ☐ En pysty syömään itse lainkaan, vaan minulle pitää antaa ravintoa letkun avulla tai suonensisäisesti.

7. Puhuminen

- 1 ☐ Pystyn puhumaan normaalisti eli selvästi, kuuluvasti ja sujuvasti.
- 2 ☐ Puhuminen tuottaa minulle pieniä vaikeuksia, esim. sanoja on etsittävä tai ääni ei ole riittävän kuuluva tai se vaihtaa korkeutta.
- 3 ☐ Pystyn puhumaan ymmärrettävästi, mutta katkonaisesti, ääni vavisten, sammaltaen tai änkyttäen.
- 4 ☐ Muilla on vaikeuksia ymmärtää puhettani.
- 5 ☐ Pystyn ilmaisemaan itseäni vain elein.

8. Eritystoiminta

- 1 ☐ Virtsarakkoni ja suolistoni toimivat normaalisti ja ongelmitta.
- 2 ☐ Virtsarakkoni ja/tai suolistoni toiminnassa on lieviä ongelmia, esim. minulla on virtsaamisvaikeuksia tai kova tai löysä vatsa.
- 3 ☐ Virtsarakkoni ja/tai suolistoni toiminnassa on melkoisia ongelmia, esim. minulla on satunnaisia virtsanpidätysvaikeuksia tai vaikea ummetus tai ripuli.
- 4 ☐ Virtsarakkoni ja/tai suolistoni toiminnassa on suuria ongelmia, esim. minulla on säännöllisesti "vahinkoja" tai peräruiskeiden tai katetroinnin tarvetta.
- 5 ☐ En hallitse lainkaan virtsaamista ja/tai ulostamista.

9. Tavanomaiset toiminnot

- 1 ☐ Pystyn suoriutumaan normaalisti tavanomaisista toiminnoista (esim. ansiotyö, opiskelu, kotityö, vapaa-ajan toiminnot).
- 2 ☐ Pystyn suoriutumaan tavanomaisista toiminnoista hieman alentuneella teholla tai pienin vaikeuksin.
- 3 ☐ Pystyn suoriutumaan tavanomaisista toiminnoista huomattavasti alentuneella teholla tai huomattavin vaikeuksin tai vain osaksi.
- 4 ☐ Pystyn suoriutumaan tavanomaisista toiminnoista vain pieneltä osin.
- 5 ☐ En pysty suoriutumaan lainkaan tavanomaisista toiminnoista.

**10. Henkinen toiminta**

- 1 ☐ Pystyn ajattelemaan selkeästi ja johdonmukaisesti ja muistini toimii täysin moitteettomasti.
- 2 ☐ Minulla on lieviä vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai muistini ei toimi täysin moitteettomasti.
- 3 ☐ Minulla on melkoisia vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on jonkin verran muistinmenetystä.
- 4 ☐ Minulla on suuria vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on huomattavaa muistinmenetystä.
- 5 ☐ Olen koko ajan sekaisin ja vailla ajan tai paikan tajua.

11. Vaivat ja oireet

- 1 ☐ Minulla ei ole mitään vaivoja tai oireita, esim. kipua, särkyä, pahoinvointia, kutinaa jne.
- 2 ☐ Minulla on lieviä vaivoja tai oireita, esim. lievää kipua, särkyä, pahoinvointia, kutinaa jne.
- 3 ☐ Minulla on melkoisia vaivoja tai oireita, esim. melkoista kipua, särkyä, pahoinvointia, kutinaa jne.
- 4 ☐ Minulla on voimakkaita vaivoja tai oireita, esim. voimakasta kipua, särkyä, pahoinvointia, kutinaa jne.
- 5 ☐ Minulla on sietämättömiä vaivoja ja oireita, esim. sietämätöntä kipua, särkyä, pahoinvointia, kutinaa jne.

12. Masentuneisuus

- 1 ☐ En tunne itseäni lainkaan surulliseksi, alakuloiseksi tai masentuneeksi.
- 2 ☐ Tunnen itseni hieman surulliseksi, alakuloiseksi tai masentuneeksi.
- 3 ☐ Tunnen itseni melko surulliseksi, alakuloiseksi tai masentuneeksi.
- 4 ☐ Tunnen itseni erittäin surulliseksi, alakuloiseksi tai masentuneeksi.
- 5 ☐ Tunnen itseni äärimmäisen surulliseksi, alakuloiseksi tai masentuneeksi.

13. Ahdistuneisuus

- 1 ☐ En tunne itseäni lainkaan ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
- 2 ☐ Tunnen itseni hieman ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
- 3 ☐ Tunnen itseni melko ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
- 4 ☐ Tunnen itseni erittäin ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
- 5 ☐ Tunnen itseni äärimmäisen ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

14. Energisyys

- 1 ☐ Tunnen itseni terveeksi ja elinvoimaiseksi.
- 2 ☐ Tunnen itseni hieman uupuneeksi, väsyneeksi tai voimattomaksi.
- 3 ☐ Tunnen itseni melko uupuneeksi, väsyneeksi tai voimattomaksi.
- 4 ☐ Tunnen itseni erittäin uupuneeksi, väsyneeksi tai voimattomaksi, lähes "loppuun palaneeksi".
- 5 ☐ Tunnen itseni äärimmäisen uupuneeksi, väsyneeksi tai voimattomaksi, täysin "loppuun palaneeksi".

15. Sukupuolielämä

- 1 ☐ Terveystilani ei vaikeuta mitenkään sukupuolielämääni.
- 2 ☐ Terveystilani vaikeuttaa hieman sukupuolielämääni.
- 3 ☐ Terveystilani vaikeuttaa huomattavasti sukupuolielämääni.
- 4 ☐ Terveystilani tekee sukupuolielämäni lähes mahdottomaksi.
- 5 ☐ Terveystilani tekee sukupuolielämäni mahdottomaksi.



EORTC QLQ-C30 (VERSION 3.0.)



Selvitämme kyselyssämme joitakin teitä ja terveyttänne koskevia asioita. Pyydämme teitä vastaamaan itse kaikkiin kysymyksiin ympäröimällä parhaiten sopiva numero. Tässä kyselyssä ei ole "oikeita" eikä "väärä" vastauksia. Pidämme antamanne tiedot ehdottoman luottamuksellisina.

	Ei lainkaan	Vähän	Melko paljon	Hyvin paljon
1. Tuntuvatko rasittavat työt kuten painavan ostoskassin tai matkalaukun kantaminen teistä työläältä?	1	2	3	4
2. Tuntuvatko <u>pitkät</u> kävelymatkat työläiltä?	1	2	3	4
3. Tuntuvatko <u>lyhyet</u> kävelymatkat kotinne ulkopuolella työläiltä?	1	2	3	4
4. Pitääkö teidän pysytellä levolla tai istumassa päivän mittaan?	1	2	3	4
5. Tarvitsetteko apua ruokaillessanne, pukeutuessanne, peseytyessänne tai WC:n käytössä?	1	2	3	4
Kuluneella viikolla:				
	Ei lainkaan	Vähän	Melko paljon	Hyvin paljon
6. Oliko teillä vaikeuksia suoriutua työstänne tai muista päivittäisistä toimistanne?	1	2	3	4
7. Oliko teillä rajoituksia harrastus- tai muissa vapaa-ajan toiminnoissanne?	1	2	3	4
8. Oliko teillä hengenahdistusta?	1	2	3	4
9. Oliko kipuja?	1	2	3	4
10. Tunsitteko levontarvetta?	1	2	3	4
11. Oliko unettomuutta?	1	2	3	4
12. Tunsitteko heikotusta?	1	2	3	4
13. Oliko ruokahaluttomuutta?	1	2	3	4
14. Oliko pahoinvointia?	1	2	3	4
15. Oksensitteko?	1	2	3	4

**Kuluneella viikolla:**

	Ei lainkaan	Vähän	Melko paljon	Hyvin paljon
16. Oliko ummetusta?	1	2	3	4
17. Oliko ripulia?	1	2	3	4
18. Olitteko väsynyt?	1	2	3	4
19. Häiritsikö kipu päivittäisiä toimianne?	1	2	3	4
20. Oliko teillä keskittymisvaikeuksia esim. sanomalehteä lukiessanne tai televisiota katsellessanne?	1	2	3	4
21. Olitteko jännittynyt?	1	2	3	4
22. Olitteko huolestunut?	1	2	3	4
23. Olitteko ärtynyt?	1	2	3	4
24. Olitteko masentunut?	1	2	3	4
25. Oliko teidän vaikea muistaa asioita?	1	2	3	4
26. Häiritsikö hoito tai fyysinen kuntonne <u>perhe-elämäännne</u> ?	1	2	3	4
27. Häiritsikö hoito tai fyysinen kuntonne <u>sosiaalista kanssakäymistä</u> ?	1	2	3	4
28. Aiheuttaako fyysinen kuntonne tai hoito taloudellisia vaikeuksia?	1	2	3	4

Vastatkaa seuraaviin kysymyksiin ympyröimällä numerosarjasta 1-7 teihin parhaiten sopiva vaihtoehto29. Millainen yleinen terveydentilanne oli kuluneella viikolla?

1	2	3	4	5	6	7
Erittäin huono			Erinomainen			

30. Millainen yleinen elämännne laatu oli kuluneella viikolla?

1	2	3	4	5	6	7
Erittäin huono			Erinomainen			



TERVEYSKYSELY EQ-5D

Olkaa hyvä ja merkitkää rastilla (x), yksi rasti kunkin alla olevan ryhmän kohdalle, mikä väitteistä kuvaa parhaiten terveydentilaanne tänään:

Liikkuminen

- ☐ Minulla ei ole vaikeuksia kävelemisessä
- ☐ Minulla on jonkin verran vaikeuksia kävelemisessä
- ☐ Olen vuoteenomana

Itsestään huolehtiminen

- ☐ Minulla ei ole vaikeuksia huolehtia itsestäni
- ☐ Minulla on jonkin verran vaikeuksia peseytyä tai pukeutua itse
- ☐ En kykene peseytymään tai pukeutumaan itse

Tavanomaiset toiminnot (esim. ansiotyö, opiskelu, kotityö, vapaa-ajan toiminnot)

- ☐ Minulla ei ole vaikeuksia suorittaa tavanomaisia toimintojani
- ☐ Minulla on jonkin verran vaikeuksia suorittaa tavanomaisia toimintojani
- ☐ En kykene suorittamaan tavanomaisia toimintojani

Kivut/vaivat

- ☐ Minulla ei ole kipuja tai vaivoja
- ☐ Minulla on kohtalaisia kipuja tai vaivoja
- ☐ Minulla on ankaria kipuja tai vaivoja

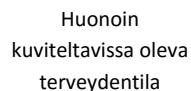
Ahdistuneisuus/Masennus

- ☐ En ole ahdistunut tai masentunut
- ☐ Olen melko ahdistunut tai masentunut
- ☐ Olen erittäin ahdistunut tai masentunut



Haluaisimme Teidän osoittavan tällä asteikolla, miten hyvä tai huono Teidän terveytenne on mielestänne tänään. Olkaa hyvä ja tehkää tämä vetämällä alla olevasta laatikosta viiva siihen kohtaan asteikolle, joka osoittaa, miten hyvä tai huono terveydentilanne on tänään.

Terveystilani tänään





TAUSTAKYSYMYKSET JA RESURSSIEN KÄYTTÖ

On tärkeää, että vastaatte **kaikkiin** 25 kysymykseen rastittamalla tai numeroin.

TAUSTATIEDOT

1. Sukupuoli

- ☐ Nainen
☐ Mies

2. Siviilisääty

- ☐ Naimaton
☐ Naimisissa
☐ Avoliitossa
☐ Leski

3. Mikä on koulutuksenne (korkein loppuun suoritettu koulutus)?

- ☐ Kansakoulu tai vähemmän
☐ Keskikoulu tai peruskoulu
☐ Ammattikoulu
☐ Lukio
☐ Opisto- tai ammattikorkeakoulutasoinen koulutus
☐ Yliopisto tai korkeakoulu

4. Mikä kuvaa parhaiten tämänhetkistä toimintaanne. Oletteko?

- ☐ Kokopäivätoisissa
☐ Osapäivätoisissa
☐ Vanhuuseläkkeellä
☐ Työkyvyttömyyseläkkeellä sairauden takia
☐ Työkyvyttömyyseläkkeellä tai varhaiseläkkeellä muun synn vuoksi
☐ Työtön
☐ Olen poissa työelämästä muun synn takia

5. Missä ammattiasemassa olette tai olette viimeksi ollut työelämässä?

- ☐ Työntekijä
☐ Alempi toimihenkilö
☐ Ylempi toimihenkilö
☐ Yrittäjä
☐ Muu
☐ En ole ollut työelämässä

6. Mikäli olette töissä, miten arvioisitte nykyisen työkykynne?

- ☐ Täysin työkykyinen
☐ Osittain työkyvytön
☐ Täysin työkyvytön

7. Mikäli olette työelämässä, kuinka monta päivää olette olleet poissa töistä viimeisen kolmen kuukauden (3 kk) aikana syövästänne johtuen?

_____ päivää viimeisen 3 kk aikana

TERVEYSPALVELUIDEN KÄYTTÖ

Kuinka usein olette käynyt viimeisen kolmen kuukauden aikana seuraavissa terveydenhoidon yksiköissä sairautenne vuoksi?

8. Lääkäriillä terveyskeskuksessa

_____ kertaa viimeisen 3 kk aikana

9. Terveydenhoitajan/sairaanhoitajan vastaanotolla terveyskeskuksessa

_____ kertaa viimeisen 3 kk aikana

10. Työpaikan työterveyslääkäriillä

_____ kertaa viimeisen 3 kk aikana

11. Työpaikan työterveyshoitajalla

_____ kertaa viimeisen 3 kk aikana

12. Yksityisellä erikoislääkäriillä

_____ kertaa viimeisen 3 kk aikana

13. Erikoislääkäriillä sairaalan poliklinikalla

_____ kertaa viimeisen 3 kk aikana



14. Erilliskäynti laboratoriossa tai röntgentutkimuksissa

_____ kertaa viimeisen 3 kk aikana

15. Kuinka monta kertaa olette viimeisen kolmen kuukauden aikana ollut sairautenne vuoksi yhteydessä puhelimitse sairaanhoitajaan tai lääkäriin?

_____ kertaa viimeisen 3 kk aikana

16. Kuinka monta kertaa olette viimeisen kolmen kuukauden aikana tavannut kotonanne sairautenne vuoksi kotisairaanhoitajan tai terveydenhoitajan?

_____ kertaa viimeisen 3 kk aikana

17. Kuinka monta kertaa viimeisen kolmen kuukauden aikana luonanne kotona on käynyt teitä hoitamassa/auttamassa kodinhoitaja tai kotiaavustaja sairautenne vuoksi?

_____ kertaa viimeisen 3 kk aikana

18. Miten paljon olette saanut hoitoa ja apua perheeltänne tai ystäviltänne sairautenne vuoksi keskimäärin viikossa viimeisen kolmen kuukauden aikana?

Keskimäärin _____ tuntia/viikossa viimeisen 3 kk aikana

Kuinka monta kertaa ja vuorokautta (vrk) olette ollut viimeisen kolmen kuukauden aikana hoidossa seuraavissa paikoissa?

19. Terveyskeskuksen vuodeosastolla

_____ kertaa yhteensä _____ vrk viimeisen 3 kk aikana

20. Keskus- tai yliopistosairaalassa

_____ kertaa yhteensä _____ vrk viimeisen 3 kk aikana

21. Muussa yleissairaalassa (aluesairaalassa)

_____ kertaa yhteensä _____ vrk viimeisen 3 kk aikana

22. Yksityisessä sairaalassa

_____ kertaa yhteensä _____ vrk viimeisen 3 kk aikana

23. Kuntoutuslaitoksessa

_____ kertaa yhteensä _____ vrk viimeisen 3 kk aikana

24. Kunnallis-/vanhainkodissa,

_____ kertaa yhteensä _____ vrk viimeisen 3 kk aikana

LÄÄKEMENOT

25. Arvio, kuinka paljon olette käyttäneet rahaa lääkkeisiin viimeisen kolmen kuukauden (3 kk) aikana?

_____ € viimeisen 3 kk aikana

Kiitos vaivannäöstänne.